MEDICAL LIBRARY

FEB 1 - 1947

Vol. 18 JANUARY, 1947 No. 1

THE JOURNAL OF ALLERGY

EDITORIAL BOARD

H. L. ALEXANDER, Editor
St. Louis

M. M. ALBERT
Brooklyn

J. H. BLACK
Dallas

M. B. COHEN
Cleveland

R. A. COOKE
New York

S. M. FEINBERG
Chicago

S. B. HOOKER
Boston

F. C. LOWELL
Boston

F. M. RACKEMANN
Boston

W. B. SHERMAN
New York

F. A. SIMON
Louisville

M. B. SULZBERGER
New York

L. TUFT
Philadelphia

M. WALZER
Brooklyn

Official Organ of AMERICAN ACADEMY OF ALLERGY

PUBLISHED BI-MONTHLY BY THE C. V. MOSBY COMPANY
ST. LOUIS 3, U. S. A.

Copyright 1947 by The C. V. Mosby Company

CONTENTS ON INSIDE COVER

Including ALLERGY ABSTRACTS

The Journal of Allergy

CONTENTS FOR JANUARY, 1947

AMERICAN ACADEMY OF ALLERGY

Second Annual Meeting, Chicago, Ill.,
Dec. 10 and 11, 1945

(*Concluded*)

Symposium on Histamine Azoprotein

Histamine Azoprotein: Clinical Evaluation. Harold D. Dundy, M.D., Benjamin Zohn, M.D., and Robert Chobot, M.D., New York, N. Y. ---- 1

Histamine Azoprotein in the Treatment of Allergy. Milton B. Cohen, M.D., and Harold J. Friedman, M.D., Cleveland, Ohio ---- 7

Clinical and Serologic Study of Ragweed Hay Fever Patients Treated with Histamine Azoprotein (Hapamine). Selian Hebald, M.D., Robert A. Cooke, M.D., and Lillian M. Downing, A.B., New York, N. Y. ---- 13

The Treatment of Asthma by Inhalation of Aerosol of Aminophyllin. Samuel J. Prigal, M.D., Alan M. Brooks, M.D., and Raymond Harris, M.D., New York, N. Y. ---- 16

Influence of Soybean Products on the Iodine Number of the Plasma Lipids and the Course of Eczema. Albert V. Stoesser, M.D., Ph.D., Minneapolis, Minn. ---- 29

Original Articles

The Effect of Beta-Dimethylaminoethyl-Benzhydryl-Ether-Hydrochloride on the Histamine Threshold of Human Skin. Milton B. Cohen, M.D., Harold J. Friedman, M.D., Jonathan Zonis, M.D., Meade Burke, M.D., and Lewis E. Abram, M.D., Cleveland, Ohio 32

The Prediction of Constitutional Reactions by Testing With Ragweed Pollen Fractions. Jonathan Zonis, M.D., Boston, Mass., and Nathan Rubin, M.D., Canton, Ohio ---- 36

Loeffler's Syndrome. Isadore M. Alpher, M.D., Washington, D. C. ---- 39

A Case of Contact Dermatitis of the Eczematous Type Resulting From Sensitization to Natural Animal Hair. Adolph Rostenberg, Jr., M.D., Chicago, Ill. ---- 47

Allergic Parotitis. George L. Waldbott, M.D., John J. Shea, M.D., Detroit, Mich. ---- 51

Concerning Reliability and Unreliability of Dried Pollen From Commercial Sources. Ralph V. Ellis, M.D., Greensboro, N. C., and A. Orville Dahl, Ph.D., Minneapolis, Minn. ---- 55

Special Report

The Pathogenesis of Infantile Eczema. Lewis Webb Hill, M.D., Boston, Mass. ---- 60

Editorial

Annual Meeting of Editorial Board ---- 70

American Academy of Allergy

News and Notes ---- 71

Book Reviews

Book Reviews ---- 80

Allergy Abstracts

Asthma and Hay Fever—Dermatology—Otorhinology and Opthalmology—Miscellaneous Allergies—Anaphylaxis—Miscellaneous--- 1-12

Vol. 18, No. 1, January, 1947. The Journal of Allergy is published Bi-monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, $7.50; In Canada and other Foreign Countries, $8.00. Entered as Second-Class Matter, November 15, 1929, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

Medical
Papers

The Journal of Allergy

VOL. 18 JANUARY, 1947 No. 1

American Academy of Allergy

Second Annual Meeting, Chicago, Ill., Dec. 10 and 11, 1945

(Concluded)

Symposium on Histamine Azoprotein

HISTAMINE AZOPROTEIN: CLINICAL EVALUATION*†

HAROLD D. DUNDY, M.D., BENJAMIN ZOHN, M.D., AND ROBERT CHOBOT, M.D.
NEW YORK, N. Y.

SEVERAL favorable reports have appeared recently on the value of histamine azoprotein in the treatment of varied allergic disorders. Moreover, immunologic evidence has been presented that it diminished the whealing capacity of the skin to histamine.[1]

We wish to report our clinical experiences with this product.

Inasmuch as results with histamine desensitization have been disappointing, it has been argued that failure might be due to the nonantigenicity of histamine. Fell, Rodney, and Marshall[2] in 1943 produced an antigenic compound by conjugating histamine with a despeciated horse-serum globulin through an azo-linkage (histamine azoprotein). In this complex, histamine acted as a hapten. Sheldon, Fell, Johnston, and Howes[3] in 1941 reported a series of 39 cases treated with histamine azoprotein. The findings in 31 were listed: 19 with fair to excellent results, 12 without benefit. Improvement was most evident in patients with contact dermatitis, atopic eczema, or allergy to physical agents. Moreover, immunologic evidence was presented by Cohen and Friedman[1] (1944) in which was demonstrated diminution of the whealing response of the skin to histamine by the administration of histamine azoprotein.

PROCEDURE

We studied a series of 40 cases: 20 children and 20 adults.

Among the children were 9 whose major disorder was atopic eczema; 9 with bronchial asthma; one with allergic rhinitis; and one with papular urticaria (Table I). Only those with a moderate or marked skin reaction to histamine were chosen for treatment. These children were tested intradermally with 0.05 c.c. of freshly prepared serial dilutions of histamine diphosphate 1:10,000, 1:100,000, 1:500,000, and 1:1,000,000. All cases were retested one week later with freshly prepared dilutions.

*From the Pediatric Allergy Clinic, Department of Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University.

†Read before the Second Annual Meeting of the American Academy of Allergy, Chicago, Ill., Dec. 11, 1945.

TABLE I. CLINICAL RESULTS WITH HISTAMINE AZOPROTEIN

CASE	INITIALS	AGE (YR.) SEX	DIAGNOSIS	HISTAMINE* SKIN REACTIONS		HAPAMINE			CLINICAL RESULTS	REACTIONS
				BEFORE TREATMENT	AFTER TREATMENT	NUMBER OF INJECTIONS	TOP DOSE (C.C.)	TOTAL (C.C.)		
1	D. H.	12 F	Allergic eczema	1—Neg 2—Sl 3—Mod 4—Mod +	Sl Sl + Mod Mod +	14	1	6.4	Unchanged	None
2	H. G.	8 F	Allergic eczema, allergic rhinitis	1—Sl + 2—Mod 3—Mod + 4—Mkd	Sl Sl + Mod Mkd	11	1	4.4	Unchanged	None
3	M. S.	14 M	Allergic eczema, ragweed hay fever	1—Sl + 2—Mod 3—Mod 4—Mkd	Sl Mod Mod + Mkd	11	1	5.5	Improved	None
4	L. P.	9 F	Allergic eczema	1—Sl 2—Sl + 3—Mod 4—Mkd	Sl Sl Mod Mkd	10	0.6	3.7	Unchanged	None Recurrent nausea and vomiting
5	T. S.	11 M	Allergic eczema, bronchial asthma	1—Neg 2—Sl 3—Mod 4—Mkd	Neg Sl Mod Mkd	14	1	8.9	Unchanged	
6	J. G.	13 F	Allergic eczema	1—Neg 2—Sl 3—Mod 4—Mkd	Neg Sl Mod Mkd	11	1	7.5	Slight improvement	None
7	D. V.	12 M	Allergic eczema, bronchial asthma	1—Neg 2—Sl 3—Mod 4—Mkd	Neg Neg Sl Mod	12	1	6.1	Slight improvement	None
8	T. M.	9 F	Allergic eczema	1—Sl 2—Sl + 3—Mkd 4—Mkd +	Neg Sl + Mod Mkd	12	1	7.2	Slight improvement	None
9	L. R.	8 M	Allergic eczema, bronchial asthma	1—Neg 2—Sl 3—Mod 4—Mod +	Neg Neg Mod Mod	9	0.8	4.2	Unchanged	None

*1, Histamine 1/1,000,000.
2, Histamine 1/500,000.
3, Histamine 1/100,000.
4, Histamine 1/10,000.

10	M. M.	12 F	Allergic rhinitis	1—Sl 2—Sl + 3—Mod 4—Mkd	Sl Mod Mod + Mkd	14	1	7.2	Unchanged	None
11	P. Q.	8 M	Bronchial asthma	1—Sl + 2—Mod 3—Mod + 4—Mkd	Sl Sl + Mod Mod +	11	1	5.5	Unchanged	None
12	P. K.	10 F	Bronchial asthma, allergic rhinitis	1—Sl 2—Mod 3—Mod 4—Mkd	Sl Mod Mod Mod +	11	1	5.5	Unchanged	None
13	L. G.	6 M	Bronchial asthma	1—Sl 2—Sl + 3—Mkd 4—Mkd	Sl Sl Mod Mod +	11	1	5.5	Unchanged	None
14	F. C.	7 M	Bronchial asthma, ragweed hay fever	1—Sl 2—Sl + 3—Mod 4—Mkd	Sl Sl Mod Mkd	11	1	5.5	Unchanged	None
15	C. A.	12 M	Bronchial asthma	1—Neg 2—Sl 3—Mod 4—Mkd	Neg Sl Mod Mkd	11	1	6.4	Unchanged	None
16	G. P.	10 F	Bronchial asthma, allergic rhinitis	1—Neg 2—Sl 3—Mod 4—Mod	Sl Sl + Mod Mod	11	1	6.2	Unchanged	None
17	S. L.	10 M	Bronchial asthma, ragweed hay fever	1—Neg 2—Sl 3—Mod 4—Mkd	Neg Sl Mod Mkd	13	0.6	4.8	Unchanged	Large locals
18	H. F.	11 F	Bronchial asthma	1—Neg 2—Sl 3—Mod 4—Mkd	Neg Sl Sl + Mod	11	1	6.2	Unchanged	None
19	J. K.	13 M	Bronchial asthma	1—Sl 2—Sl 3—Mod 4—Mkd	Neg Sl Mod Mod	10	1	6.4	Unchanged	None
20	G. S.	3 M	Papular urticaria	1—Sl 2—Mod 3—Mod 4—Mkd	Sl Mod Mod Mkd	11	1	5.5	Improved	None

Therapy was instituted with histamine azoprotein by subcutaneous injection, beginning with 0.05 c.c. and increasing weekly by 0.1 c.c. until a maximum dose of 1 c.c. was reached where possible. Intradermal tests with histamine diphosphate were repeated at the conclusion of the course of injections for comparison. During this period no local or other parenteral therapy was used.

The group of 20 adults included 9 with allergic rhinitis, 3 with infective bronchial asthma, 4 with migraine, 2 with angioneurotic edema, and 2 with pollinosis (Table II). They were selected for trial with histamine azoprotein because of their poor response to standard allergic measures. They were treated by one of the authors (H.D.D.) with the drug in conjunction with other allergic therapeutic measures, including pollen, inhalant, and vaccine therapy.

RESULTS

We failed to find any appreciable change in the whealing response of the skin to histamine (Table I). Serial dilutions of histamine produced wheals identical in size before and after treatment with histamine azoprotein. Clinically, in 4 of the 9 cases of eczema and in the case of papular urticaria, slight improvement was noted (Table I). There were two treatment reactions among the 20 children: treatment of one of them had to be discontinued because he vomited regularly within two hours of injection; in the other, the drug was stopped because of recurrent marked local reactions.

Of the 20 adults, 6 showed slight improvement. Two of these had migraine, 2 had angioneurotic edema, and 2 had allergic rhinitis. Treatment of 2 of these with the drug was stopped because of untoward reactions, both local and general. In one, there developed a marked swelling of the arm and forearm, associated with elevation of temperature for sixty hours. On subsequent administration of 0.1 c.c., a milder reaction of the same type was again apparent. In the other, recurrent large local reactions necessitated discontinuance of treatment.

Of the 40 cases investigated, slight improvement was noted in 11. However, not one of these showed a completely satisfactory result. The possibility of spontaneous remission, or the psychic effect of a new therapeutic measure as an etiological factor in improvement, cannot be excluded.

DISCUSSION

Dale and Laidlow, in their original investigations in 1910, reported that "the immediate symptoms with which an animal responded to an injection of a normally inert protein to which it has been sensitized are to a large extent those of poisoning by 'histamine.'" By 1929, Dale [5] visualized anaphylactic shock as the result of cellular injury due to antigen-antibody reaction in which histamine is liberated and its effects are prominent.

Dragstedt[6] admits that "there is a legitimate basis for skepticism regarding the role of histamine in anaphylaxis." In reviewing the extensive literature on histamine in anaphylaxis, he points out that it is found as a normal constituent of various animal tissues, as established by Best and his associates.[7] Histamine can mimic many of the important anaphylactic reactions and is present in the tissues where these reactions occur. Dragstedt and Gebauer-Fuelnegg[8] showed that the anaphylactic reaction in the dog was accompanied by the appearance, in the thoracic duct and the blood, of a smooth muscle contracting

TABLE II

CASE	INITIALS	AGE (YR.) SEX	ONSET AGE (YR.)	DIAGNOSIS	HAPAMINE NUMBER OF INJECTIONS	HAPAMINE TOP DOSE (C.C.)	HAPAMINE TOTAL DOSE (C.C.)	RESULTS	REACTIONS
21	Y. F.	36 F	20	Allergic rhinitis	22	0.25	5.0	Unchanged	None
22	P. F.	58 F	38	Allergic rhinitis	14	0.4	3.5	Unchanged	None
23	F. G.	31 F	22	Allergic rhinitis, asthma	16	0.5	4.9	Unchanged	None
24	R. G.	33 F	31	Allergic rhinitis	26	0.25	4.8	Unchanged	None
25	N. R.	42 F	40	Allergic rhinitis	22	1.0	17.0	Unchanged	None
26	V. R.	34 F	30	Allergic rhinitis, physical allergy	11	1.0	5.4	Improved	None
27	L. R.	37 F	10	Allergic rhinitis	12	0.3	3.2	Unchanged	Large locals
28	H. S.	27 F	22	Allergic rhinitis					
29	D. S.	18 M	9	Allergic rhinitis	18	0.25	4.9	Improved	None
30	R. B.	40 F	35	Bronchial asthma—infective	20	1.0	15.3	Unchanged	None
31	L. S.	52 M	44	Bronchial asthma—infective	20	1.0	16.4	Unchanged	None
32	J. M.	42 M	41	Bronchial asthma—infective	22	1.0	15.0	Improved	None
33	P. E.	37 M	36	Migraine, ragweed hay fever	15	0.5	6.5	Unchanged	None
34	C. K.	31 F	8	Migraine, ragweed hay fever	11	1.0	5.0	Improved	None
35	M. P.	25 M	4	Migraine	18	0.25	3.8	Unchanged	None
36	A. S.	43 F	30	Migraine, ragweed hay fever	17	0.7	6.8	Unchanged	Large local fever
37	H. F.	16 F	11	Angioedema	16	0.5	7.0	Unchanged	None
38	M. S.	30 F	30	Angioedema	11	0.5	4.5	Improved	None
39	G. M.	31 F	25	Hay fever, allergic rhinitis	17	0.25	4.4	Improved	None
					27	1.0	20.0	Unchanged	None
40	B. S.	37 F	22	Hay fever, allergic rhinitis	22	1.0	15.0	Unchanged	None

substance with many of the characteristics of histamine. Similarly, Bartosch, Feldberg, and Nagel[9] showed that perfusion of antigen through the isolated lungs of sensitized guinea pigs yielded a similar smooth muscle-contracting substance.

Techniques have been developed for the quantitative analysis of histamine in the blood by biologic assay using smooth muscle contractions as their base (Barsoum and Gaddum,[10] Code[11]).

Histamine has been demonstrated in human tissues; its administration has caused the duplication of many allergic reactions; its blood level is frequently increased during allergic reactions; its pharmacologic properties can account for some allergic phenomena. Along such lines has the evidence for the importance of histamine in anaphylaxis been presented (Dragstedt[12]).

Contrary evidence appears in the studies of Campbell and Nicoll,[13] who showed that rat uteri "unaffected by ordinary doses of histamine, responded in their tissue bath to some substance released by sensitized guinea-pig lung tissue during anaphylactic shock." It is apparent that some nonhistamine substance was released. In this connection, Schild[14] concluded that histamine released from the cell either has a different action from that of histamine applied to the cell surface, or plays only a secondary part in anaphylactic shock.

Cooke[15] presented experimental evidence in which he shocked a sensitized guinea pig uterine horn with histamine until it failed to contract, with his-

tamine remaining in the bath. When the horn had relaxed, antigen was added, and a prompt and maximal contraction occurred. Cooke could find no unresponsive phase in urticaria, no increase of tolerance to histamine, no clinical results with chronic urticaria, and no evidence that histamine is increased in the blood during general allergic reactions. He believes, therefore, that a critical and even a skeptical point of view is still warranted, both as to the role of histamine in allergy and as to the therapeutic benefit to be derived.

The evidence we have presented does not bear out the therapeutic efficacy or the immunologic specificity of histamine azoprotein. Our clinical results with the drug are as disappointing as they have been with histamine. Moreover, despite the reported claims of absent local or constitutional reactions, we found a significant number of both. We have been unable to confirm the reported decrease in the whealing capacity of the skin to histamine subsequent to the administration of histamine azoprotein. Hence, we cannot as yet subscribe to its therapeutic usefulness.

SUMMARY

1. Treatment with histamine azoprotein was generally ineffective in a series of 40 allergic individuals.

2. Significant reactions, local and general, were noted in 10 per cent of the patients.

3. The whealing capacity of the skin to histamine was unimpaired following treatment with histamine azoprotein.

REFERENCES

1. Cohen, M. B., and Friedman, H. J.: Immunity Against H-Substance, J. ALLERGY **15**: 245, 1944.
2. Fell, N., Rodney, G., and Marshall, D. E.: Histamine-Protein Complexes: Synthesis and Immunologic Investigation. I. Histamine Azo-Protein, J. Immunol. **47**: 237, 1943.
3. Sheldon, N. M., Fell, N., Johnston, N. H., and Howes, H. A.: A Clinical Study of Histamine Azo-Protein in Allergic Diseases (A Preliminary Report), J. ALLERGY **13**: 18, 1941.
4. Dale, H. H., and Laidlow, P. P.: The Physiological Action of B-Iminazolytethylamine, J. Physiol. **41**: 318, 1911.
5. Dale, H. H.: Croonian Lectures on Some Chemical Factors in the Control of the Circulation, Lancet **216**: 1285, 1929.
6. Dragstedt, C. A.: Significance of Histamine in Anaphylaxis, J. ALLERGY **16**: 69, 1945.
7. Best, C. H., Dale, H. H., Dudley, H. W., and Thorpe, W. V.: The Nature of the Vaso-Dilator Constituents of Certain Tissue Extracts, J. Physiol. **62**: 397, 1927.
8. Dragstedt, C. A., and Gebauer-Fuelnegg, E.: Studies in Anaphylaxis I. The Appearance of a Physiologically Active Substance During Anaphylactic Shock, Am. J. Physiol. **102**: 512, 1932. II. The Nature of a Physiologically Active Substance Appearing During Anaphylactic Shock, Ibid. **102**: 520, 1932.
9. Bartosch, R., Feldberg, W., and Nagel, E.: Pflüger's Arch. f. d. ges. Physiol. **230**: 129, 1932.
10. Barsoum, G. S., and Gaddum, J. H.: The Pharmacological Estimation of Adenosine and Histamine in Blood, J. Physiol. **85**: 1, 1935.
11. Code, C. F.: The Quantitative Estimation of Histamine in the Blood, J. Physiol. **89**: 257, 1937.
12. Dragstedt, C. A.: Significance of Histamine in Anaphylaxis and Allergy, Quart. Bull., Northwestern Univ. M. School **17**: 102, 1943.
13. Campbell, D. H., and Nicoll, P. A.: Studies on In Vitro Anaphylaxis and Release of an Active Non-Histamine Material From Sensitized Guinea-Pig Lung, J. Immunol. **39**: 103, 1940.
14. Schild, A.: The Reaction of the Guinea Pig's Uterus Immersed in a Histamine Solution to Histamine and Anaphylaxis, J. Physiol. **86**: 51P, 1936.
15. Cooke, R. A.: Protein Derivatives as Factors in Allergy, Ann. Int. Med. **16**: 71, 1942.

(For Discussion, see p. 15)

HISTAMINE AZOPROTEIN IN THE TREATMENT OF ALLERGY

MILTON B. COHEN, M.D.,*† AND HAROLD J. FRIEDMAN, M.D., CLEVELAND, OHIO

THE reaction in the clinical allergies results from the contact of an antigen with the specific antibodies in the cells of the affected tissue. This reaction is the same pathologically and physiologically no matter what the antigen may be. Whether one has asthma on exposure to ragweed or grass pollen, on the inhalation of house dust, or on the ingestion of egg, the resultant reactions will be indistinguishable and the symptoms will be identical. This identity of reaction following exposure to a wide variety of chemically different antigens can be explained only by the assumption that some common toxic substance is freed from the tissues as a result of the antigen antibody union.

The exact nature of this toxic substance has not as yet been determined conclusively, but there is very good evidence that histamine or some substance pharmacologically indistinguishable from histamine plays a major role in these reactions.

Dragstedt[1] has shown that all of the symptoms of *shock* which occur during anaphylaxis in the dog can be explained by the amount of histamine which can be recovered from the blood of the dog. Katz and Cohen[2] have demonstrated that human blood cells from ragweed-sensitive persons release measurable amounts of histamine in vitro when exposed to ragweed antigen, and Katz[3] has furthermore shown that histamine is released from the wheal in intradermal skin test sites.

The relative importance of histamine in allergic reactions and its relationship to H-substance could be determined if there were available some histamine antagonists which were powerful enough to neutralize the amount of histamine produced in a given reaction or to inhibit all of its effects.

In 1941, Fell and his associates[4] conjugated histamine to despeciated horse globulin to form histamine azoprotein and reported that guinea pigs immunized with this substance were protected significantly against anaphylactic shock. They reported further that immunized rabbits developed precipitins against the histamine portion of the antigen.

Further confirmation of these immunologic findings was reported for human beings by Cohen and Friedman,[5] who showed, in addition, that immunization with histamine azoprotein was followed by an increased tolerance for histamine as measured by the iontophoretic skin test threshold. Furthermore, the sera of treated persons specifically neutralized histamine in vitro, and the neutralization occurred speedily and was not delayed as is the case with histaminase.

Having used approximately 3 liters of histamine azoprotein in human begins during the past several years, we now desire to record our clinical experiences.

---

*From the Asthma and Hay Fever Clinic and the Allergy Clinic, Mt. Sinai Hospital, Cleveland, Ohio.

†Read at the Second Annual Meeting of the American Academy of Allergy, Chicago, Ill., Dec. 11, 1945.

Dosage.—In order to obtain immunity with azoprotein, it is necessary that large amounts be given in a relatively short period of time followed by a rest period and a series of booster injections. Experience has taught us that we can begin with 0.1 ml., subcutaneously. In most patients the following schedule of increases can be given at three- to seven-day intervals.

Dose 1	0.1 ml.
Dose 2	0.5 ml.
Dose 3	1.0 ml.
Dose 4	1.0 ml.
Dose 5	1.0 ml.
Dose 6	1.0 ml.
Dose 7	1.0 ml.

In some patients, smaller doses are necessary because of marked local swelling. For these, the increases are less abrupt, but a total of at least 5 ml. is given in the first series of injections.

Following the first series of injections a rest period of two to three months is allowed, after which the second series is given as nearly as possible in accordance with the following schedule:

Dose 1	0.1 ml.
Dose 2	0.5 ml.
Dose 3	1.00 ml.
Dose 4	1.00 ml.

During the administration of the second series of doses more patients will require changes in the dosage schedule due to local swelling. In any event the second series should not be stopped until a total of at least 2.5 ml. has been given. If the patient does well on histamine azoprotein, a third and sometimes a fourth series of doses is given after a rest period comparable to the one between the first and second series.

Reactions.—We have encountered only two patients who had generalized reactions. In these, all of the signs of histamine intoxication occurred within fifteens minutes following the first injection of 0.1 milliliter. The histamine-azoprotein was tested for free histamine, and none was found. We concluded that these individuals had the ability to free histamine rapidly from the complex and therefore gave them no further treatment with the drug.

Following the first injection of histamine-azoprotein, there is usually an area of redness and induration about 3 cm. in diameter which lasts twenty-four hours. Following subsequent injections, the area of induration may be as large as the palm of the hand and may last forty-eight to seventy-two hours. There are usually no symptoms other than tenderness over the swollen area. Occasionally there is slight malaise and very low-grade fever. Local reactions of the type just described are ignored. In about 10 per cent of patients receiving the first series and in about 20 per cent of those receiving the second series of injections larger local reactions occur. Such reactions necessitate a

smaller increase in dosage or a repetition of the preceding dose until the usual reaction takes place. In five patients there has been an elevation of temperature to 101° F. with brawny induration of the arm and enlargement of and tenderness over the glands in the axilla which lasted seven days. All cleared up completely without complications.

Histamine Neutralization in Treated Patients.—Untreated patients, and nonallergic persons as well, react to histamine by iontophoresis at the same level when a technique using a 1 sq. cm. electrode, 1 ma. of current, and five minutes of time is followed. This threshold of reaction is a dilution of histamine acid phosphate in saline representing a dilution of 1:6,400,000 of histamine base. In our earlier work we used histamine solutions which were kept in rubber stoppered bottles for months at a time and found that the threshold reaction using our standard technique varied considerably. Further study and consultation with workers who were quantitating histamine biologically elucidated our problem. It is necessary to make fresh histamine solutions and dilutions for each test, and these solutions must not be allowed to stand more than an hour or two. When these precautions are followed, the threshold can be demonstrated regularly to be 1:6,400,000, as described previously.

After the first series of injections is completed, the average case has a histamine threshold of from 1:3,200,000 to 1:1,600,000. After the booster series the threshold varies from 1:1,600,000 to 1:200,000.

It can be readily seen from these observations that no significant result can be expected from treatment with this drug until the end of the booster series of injections, a period of from three to four months after the beginning of the treatment. Furthermore, the amount of protection obtainable against histamine is small in comparison with the amount which is released in an allergic reaction. We have estimated that the greatest protection obtainable could neutralize only 15 to 20 per cent of the histamine released in a severe allergic reaction. Obviously, therefore, immunization with histamine azoprotein cannot be expected to replace avoidance of allergens, or specific treatment with them in addition to their avoidance. It should be useful as an adjunct in otherwise well-managed cases of undetermined etiology where ordinary avoidance and specific therapy cannot be carried out.

We have reviewed the records of 55 patients who have received histamine azoprotein and who are currently being followed in order to evaluate its efficiency. In all of these, general medical management, management from the allergic standpoint, and drug therapy were used. Therapy was not begun until the effects of other types of management had been observed. The results have been recorded as excellent, good, and negative.

Those recorded as excellent had periods of remission lasting several months. These periods of remission were at least twice as long as those which had occurred spontaneously since the onset of symptoms or as a result of previous management. Those recorded as good had marked to moderate improvement but did not meet the stringent requirements of the excellent group.

Table I presents our data on these cases. Table II is a summary of the material in Table I.

TABLE I

NAME	AGE (YRS.)	SEX	DIAGNOSIS	DURATION	ETIOLOGY	ML. H DOSAGE	TIME OBSERVED	RESULT
T. H.	54	F	Angioneurotic edema	6 mo.	Coal tars	3.8	6 mo.	Negative
L. W.	54	F	Urticaria	5 mo.	Coal tars	7.9	8 mo.	Excellent
R. D.	17	F	Asthma, urticaria	8 yrs.	Inhalants—foods, pollens	5.25	11 mo.	Negative
E. Z.	16	F	Urticaria	6 yrs.	Unknown	14.0	1 yr.	Excellent
R. D.	61	F	Urticaria	6 mo.	Unknown	13.0	9 mo.	Excellent
R. B.	39	M	Migraine, urticaria	20 yrs.	Coal tar	6.0	6 mo.	Good
T. W.	55	F	Angioneurotic edema	1 yr.	Coal tar	8.0	8 mo.	Good
E. H.	39	F	Urticaria	8 yrs.	Unknown	3.85	3 mo.	Negative
H. M.	50	M	Angioneurotic edema	13 yrs.	Coal tar	15.0	1 yr.	Excellent
T. R.	45	F	Urticaria	2 yrs.	Unknown	20.6	2 yrs.	Excellent
M. R.	29	F	Asthma, urticaria	7 yrs.	Coal tar ?	22.8	1 yr.	Negative
B. S.	21	F	Urticaria	3 mo.	Coal tar ?	9.6	3 yr.	Excellent
S. S.	29	F	Urticaria, angioneurotic edema	3 mo.	Coal tar ? heat	19.8	2 yrs.	Excellent
S. P.	41	F	Urticaria	1 yr.	Unknown	10 c.c.	2 yrs.	Good
H. S.	30	F	Urticaria	10 yrs.	Heat	20.5	1 yr.	Excellent
S. W.	59	M	Angioneurotic edema	6 mo.	Coal tar	9.35	5 mo.	Good
A. G.	61	F	Asthma	9 yrs.	Unknown	10.0	8 mo.	Excellent
J. L.	38	F	Asthma	1 mo.	Unknown	11.0	9 mo.	Control of asthma, no change in nasal symptoms
M. K.	51	M	Asthma	6 yrs.	Unknown	7.0	9 mo.	Excellent
F. Y.	28	M	Asthma	22 yrs.	Unknown	5.0	7 mo.	Excellent
O. K.	60	F	Asthma	4 yrs.	Unknown	9.75	7 mo.	Excellent
H. V.	52	M	Asthma	3 yrs.	Unknown	8.0	8 mo.	Excellent
L. M.	33	M	Asthma	5 yrs.	Unknown	8.5	8 mo.	Excellent
R. S.	42	M	Asthma	30 yrs.	Unknown	13.0	1 yr.	Excellent
R. D.	17	F	Asthma	8 yrs.	Pollens, foods, inhalants	5.25	11 mo.	Negative
E. LaS.	53	F	Asthma	15 yrs.	Unknown	13.3	4 mo.	Negative
J.	50	M	Asthma	24 yrs.	House dust	13.5	4 mo.	Good
G. T.	60	F	Asthma	13 yrs.	Unknown	13.5	4 mo.	Negative
I. B.	58	F	Asthma	15 yrs.	Unknown	13.1	4 mo.	Negative
F. T.	58	F	Asthma	20 yrs.	Unknown	11.6	4 mo.	Negative
M. W.	62	F	Asthma	25 yrs.	Unknown	14.3	4 mo.	Negative
I. P.	48	F	Asthma	6 yrs.	Unknown	12.3	4 mo.	Negative
A. L.	63	F	Asthma	10 yrs.	Unknown	12.4	4 mo.	Negative
J. C.	61	F	Asthma	16 yrs.	Unknown	13.3	4 mo.	Negative
E. B.	40	F	Asthma	12 yrs.	Unknown	13.8	4 mo.	Negative
C. M.	47	M	Vasomotor rhinitis	2½ yrs.	Unknown	11.0	8 mo.	Negative
J. L.	38	F	Vasomotor rhinitis	1 mo.	Unknown	11.0	9 mo.	Negative
V. B.	30	F	Vasomotor rhinitis	5 yrs.	Dust	15.0	1 yr.	Negative
N. C.	55	M	Hay fever	15 yrs.	Ragweed	10.9	2 yrs.	Negative
R. M.	12	M	Hay fever	5 yrs.	Ragweed, foods	10.9	3 yrs.	Negative
F. G.	36	F	Hay fever	10 yrs.	Ragweed	10.4	2 yrs.	Negative
C. L.	40	M	Hay fever	12 yrs.	Ragweed, foods	11.5	4 yrs.	Good
E. S.	26	M	Hay fever	18 yrs.	Ragweed, orris, house dust, foods	9.3	6 yrs.	Negative
J. R.	26	F	Hay fever	2 yrs.	Ragweed, house dust	10.5	1 yr.	Negative
M. S.	32	F	Contact eczema	11 yrs.	Undetermined	11.75	8 mo.	Excellent

TABLE I—CONT'D

NAME	AGE (YRS.)	SEX	DIAGNOSIS	DURATION	ETIOLOGY	ML. H DOSAGE	TIME OBSERVED	RESULT
N. L.	51	F	Contact eczema	4 yrs.	Handling fruits and vegetables	24.0	18 mo.	Excellent
D. R.	46	F	Contact eczema	1 yr.	Undetermined	9.0	8 mo.	Negative
M. C.	31	F	Contact eczema	9 mo.	Undetermined	12.0	6 mo.	Negative
A. S.	39	F	Contact eczema	8 yrs.	Cosmetics, cleanex	13.5	6 mo.	Negative
A. A.	21 mo.	F	Atopic eczema	18 mo.	Negative tests, unknown	12.6	1 yr.	Excellent
M. L.	20	F	Atopic eczema	14 yrs.	Foods, contactants	20.0	6 mo.	Fair
T. J.	4	F	Atopic eczema	3 yrs.	Unknown	12.5	1 yr.	Negative
M. B.	36	F	Atopic eczema	6 yrs.	Tomato and unknown	30.0	1 yr.	Cleared. Can be exacerbated by eating tomato
L. Z.	3	M	Atopic eczema, asthma	1 yr.	Foods, pollens, inhalants	5.0	2 yr.	Good
J. McK.	1	F	Atopic eczema	3 mo.	Unknown	4.2	1 yr.	Negative
J. N.	20 mo.	F	Atopic eczema	19 mo.	Foods, inhalants	5.6	10 mo.	Good

TABLE II

DIAGNOSIS	NUMBER OF CASES	RESULTS		
		EXCELLENT	GOOD	NEGATIVE
Urticaria	15	8	3	4
Asthma	19	8	1	10
Contact eczema	5	2	0	3
Atopic eczema	7	1	3	3
Vasomotor rhinitis	3	0	0	3
Hay fever	6	0	1	5
Total	55	19	8	28

DISCUSSION

It is obvious from these records that a condition like hay fever, in which the exposure to the exciting allergen is maximal, cannot be prevented by treatment with histamine azoprotein. This is in accord with the experimental observations that the amount of immunity against H-substance or histamine is insufficient to protect against the release of relatively large amounts of H-substance. In addition, we have seen the development of ragweed hay fever in a patient who had maximal immunity following treatment with histamine azoprotein.

The results obtained in chronic urticaria were most gratifying. In the days before this drug was available, we felt relatively helpless when confronted by a case of chronic urticaria which could not be proved to be due to the ingestion of some drug. Today we expect to obtain a satisfactory result in the majority using the drug as an adjunct to general medical and psychological therapy.

In asthma, we also obtained gratifying results. The cases chosen for this treatment were classed as failures following ordinary management. Any method which gives relief to half of such cases is worthy of continued use.

Since the introduction of β-dimethylaminoethyl benzhydryl ether hydrochloride, we have found this drug to be very effective in urticaria and in some cases of asthma. Our studies have indicated that this drug has a very definite antihistamine effect on the capillaries of the skin. We now give treatment with histamine azoprotein only to those patients who respond satisfactorily to preliminary treatment with this drug.

CONCLUSIONS

1. Treatment with histamine azoprotein is of distinct value in urticaria and certain cases of bronchial asthma.

2. It is of no value when used alone in the prevention of hay fever.

3. Histamine azoprotein is a poor antigen. Adequate amounts must be given to obtain the maximal immunity. It requires about four months of treatment to obtain this degree of immunity.

4. Systemic reactions rarely occurred in our experience. Large local reactions are to be expected and are harmless.

REFERENCES

1. Dragstedt, C. A.: Significance of Histamine in Anaphylaxis and Allergy, Quart. Bull., Northwestern Univ. M. School **17**: 102-107, 1943.
2. Katz, G., and Cohen, S.: Experimental Evidence for Histamine Release in Allergy, J. A. M. A. **117**: 1782-1785, 1941.
3. Katz, G.: Histamine Release in Allergic Skin Reaction, Proc. Soc. Exper. Biol. & Med. **49**: 272-277, 1942.
4. Fell, N., Rodney, G., and Marshall, D. E.: Histamine Protein Complexes: Synthesis and Immunologic Investigation, J. Immunol. **47**: 237-249, 1943.
5. Cohen, M. B., and Friedman, H. J.: Immunity Against H Substance, J. ALLERGY **15**: 274-278, 1944.

(For Discussion, see p. 15)

CLINICAL AND SEROLOGIC STUDY OF RAGWEED HAY FEVER PATIENTS TREATED WITH HISTAMINE AZOPROTEIN (HAPAMINE)*†‡

Abbreviated Report

Selian Hebald, M.D., Robert A. Cooke, M.D., and Lillian M. Downing, A.B.
New York, N. Y.

IN A recent study Fell and his co-workers[1] reported the preparation of histamine antigens by coupling diazotized p-amino-benzoyl-histamine to various proteins. They hyperimmunized animals with these compounds in an attempt to produce protection against excess histamine released by antigen-antibody reactions in anaphylaxis and allergy. It was claimed that antibodies were produced which were partially specific for the histamine haptine, and animals so immunized displayed a marked degree of resistance to anaphylaxis. It was Fell's theory that histamine azoprotein produced antibody to histamine and so neutralized the supposed histamine liberated in the allergic reaction. Cohen and Friedman[2] reported specific precipitins for histamine in patients treated with histamine azoprotein and in vitro neutralization of histamine by their sera, as well as protection of the skin against histamine introduced intradermally. The immunologic H-substance then is the supposed basis of anaphylactic shock, and, by analogy, the allergic reactions in man as well. It was surmised that an anti-histamine-antibody might prevent the liberation of intracellular histamine in such reactions.

This investigation was undertaken to determine if constitutional reactions could be prevented in ragweed hay fever patients immunized with histamine-azoprotein, to evaluate clinical benefits in patients so immunized, and to see if the specificity of the precipitins produced by such immunization was specific for the histamine haptine.

In eight patients having clinical ragweed hay fever, four were treated with whole ragweed extract and four were treated with whole ragweed extract plus fraction 1. Fraction 1 is the fraction of ragweed pollen precipitated by 50 per cent saturation with ammonium sulfate. All of these patients had had constitutional reactions in the course of their treatment at fairly definite "ceiling" levels of dosage, beyond which we could not go without again producing definite but mild constitutional reactions. Histamine azoprotein in increasing amounts was given to each patient at weekly injections, in addition to the ragweed extract which was kept below the level of dosage that produced a constitutional reaction. The total dosage of histamine azoprotein ranged from 2.3 ml. to 17 ml. for each patient in this group. We did not attempt to increase the dosage of ragweed extract to the point that had produced a constitutional reaction or go

*From Department of Allergy, The Roosevelt Hospital, New York City.

†Histamine-azoprotein (Hapamine) used in this work was donated through the courtesy of Parke Davis & Co.

‡Read at the Second Annual Meeting of the American Academy of Allergy, Chicago, Ill., Dec. 11, 1945.

beyond it, until a dosage of 2 ml. of histamine azoprotein for one injection had been reached in those patients who could take this amount. We also attempted to reach a top dosage of 2 ml. of histamine azoprotein for one injection in all patients before blood specimens were taken for precipitin determinations. It was not always possible to give this large amount in one injection. In one patient, for instance, a very large local reaction with severe pain and swelling of the axillary glands occurred following an injection of 0.6 ml. of the histamine azoprotein. In this group of eight patients, constitutional reactions with ragweed extract therapy occurred in four at the identical level of dosage both before and after treatment with histamine azoprotein. In two, reactions occurred at a higher level; while in the last two, constitutional reactions occurred at a lower level of dosage after therapy.

Direct intradermal skin tests were done on six of the patients with dilutions of histamine base, 1:1000 to 1:100,000,000. These direct skin tests were identical for all comparative dilutions both before and after histamine azoprotein therapy. Subcutaneous injections of histamine were given to six of the patients. The typical histamine response of flush, headache, and tachycardia was obtained in two with an injection of 0.05 mg. of histamine base both before and after histamine azoprotein therapy, while in four, the typical response was obtained after an injection of 0.1 mg. histamine base, both before and after therapy.

Precipitin tests to histamine azoprotein and histamine casein were done on all serums.* No precipitins were demonstrable in any serum before histamine azoprotein therapy. Precipitins to histamine azoprotein were demonstrable after therapy in five of the eight serums. No precipitins to the histamine casein were demonstrable in any serum. There was no observable clinical improvement in hay fever as a result of therapy with histamine azoprotein.

Histamine azoprotein with a total dosage of 4.4 ml. to 20 ml. was given to each of five clinically sensitive ragweed patients prior to and during the ragweed season of 1945. These patients had never been treated with ragweed extract. Precipitins to histamine azoprotein were demonstrable in four of the five patients after therapy. In no instance were precipitins demonstrable to the histamine casein. The clinical hay fever results were uniformly bad for all patients both for the ragweed season of 1944 when no therapy at all had been taken, and 1945 when histamine azoprotein alone had been received.

In all, serum studies were done on 31 patients after histamine azoprotein therapy. Of these, 21 showed precipitins to the histamine azoprotein, but in none were precipitins to the histamine casein demonstrable. There were no precipitins to histamine azoprotein in the pretreatment serums of any patients.

Six patients were given a second course of treatment with histamine azoprotein after a three-month rest period. Four of these six showed precipitins to histamine azoprotein after the first course of therapy. None of them showed precipitins to this compound after the second course of therapy. In none were precipitins to the histamine casein demonstrable.

*The histamine casein was obtained from Parke Davis & Co. through the courtesy of Dr. Fell.

In view of the fact that no precipitins were demonstrable in any serum to the histamine casein, precipitins to histamine azoprotein can only mean precipitins to the azoprotein or protein radicle. If any histamine neutralization had occurred with histamine azoprotein therapy, then precipitins to the histamine casein should have been demonstrated. We were not able to show this.

SUMMARY

1. We were not able to raise the "ceiling" dosage of ragweed extract in six of eight patients with the additional treatment of histamine azoprotein.

2. In five patients with ragweed hay fever who had never been treated before, there appeared to be no clinical benefit resulting from treatment with histamine azoprotein. In the eight patients who were treated with ragweed extract and histamine azoprotein there appeared to be no difference in the clinical result over the preceding year when ragweed extract alone had been given.

3. Skin tests with histamine dilutions and histamine response by subcutaneous injection were the same before and after treatment with histamine azoprotein.

4. In no patients were precipitins specific for the histamine radicle demonstrable after histamine azoprotein injections. All the histamine casein reactions were negative.

5. Regardless of effect in experimental animals, histamine azoprotein did not give protection against constitutional reactions nor protection against clinical allergy of hay fever types.

REFERENCES

1. Fell, N., Rodney, G., and Marshall, D. E.: Histamine-Protein Complexes; Synthesis and Immunological Investigation, J. Immunol. **47**: 237, 1943.
2. Cohen, M. B., and Friedman, H. J.: Immunity Against H-Substance, J. ALLERGY **15**: 245, 1944.

DISCUSSION

DR. LEO CRIEP, Pittsburgh, Pa.—Some day we will look back on this see-saw type of discussion on the merits of various agents very much as we look back at similar discussion on the various agents for the treatment of pernicious anemia prior to liver extract.

Dr. Cohen states he has had results with hay fever. He feels there is an expansive type of reaction and there is liberated a large amount of histamine in the atopic reaction. To my mind, the treatment of urticaria or severe reaction should be associated with as much liberation of histamine as possible.

Dr. Hebald and his associates have tried to clarify the confusion that exists concerning azoprotein. My own clinical opinion agrees with the conclusions brought out by this group. I wish to cite the case of a patient who presented a reaction to orris root and gave a positive patch test with it. She was treated over a long time with several courses of azoprotein. After this period of time not only did her clinical condition fail to improve, but the intradermal tests were the same as before treatment was instituted.

THE TREATMENT OF ASTHMA BY INHALATION OF AEROSOL OF AMINOPHYLLIN*†‡

SAMUEL J. PRIGAL, M.D., ALAN M. BROOKS, M.D., AND RAYMOND HARRIS, M.D.,
NEW YORK, N. Y.

THE use of aminophyllin in the treatment of asthma has become an established procedure since its introduction by Hermann and Aynesworth in 1937.[1] Aminophyllin intravenously may succeed in abating an attack where epinephrin has failed, and frequently alters the so-called state of "epinephrin fastness" by restoring the patient's ability to respond to this drug. Aminophyllin has been effective in the treatment of asthma when given orally, intramuscularly, intravenously, and rectally.[2] Clinical and vital capacity studies show that aminophyllin is highly effective by inhalation in aerosol form, and that it may even succeed in some cases where an intravenous injection has failed.

Segal,[3] and Barach§ treated some cases of asthma with aerosol of aminophyllin by the continuous inhalation method described by Richards, Barach, and Cromwell.[4] This method uses a special glass nebulizer with oxygen as a driving force. Because of the large volume of aminophyllin used in the aerosol treatment, the continuous inhalation method proved too cumbersome and costly, and was discontinued by these workers.

Our interest in the inhalation method for the administration of aminophyllin followed our successful formation of aerosols of epinephrin, sodium sulfadiazine, and penicillin, by a new device|| recently described elsewhere.[5, 6] This device is a combined steam generator and aerosolizer which is simple, inexpensive, and suitable for home and office use (Fig. 1). The patient quickly learns to use the apparatus for the self-administration of aminophyllin and other medications.

Briefly, the apparatus consists of a container holding water. Upon the application of electric current acting through electrodes suspended in the water, the latter is rapidly heated and converted to steam. The steam emerges from a spout which is specially designed to allow a thin trickle of the steam under pressure to pass over a tube with which it is connected at right angles, and which extends into a container holding the medication in solution. The rapid passage of the steam creates a vacuum in the tube leading to the medication, allowing the latter to be drawn up and expelled from the nozzle in a fine mist mixed with the steam. Other features include a safety valve to reduce excessive pres-

*From the Department of Medicine (Allergy), New York Medical College Flower-Fifth Avenue Hospitals, Metropolitan Hospital, N. Y. C., and from the Allergy Clinic of the New York Post Graduate Hospital.

†Read at the Second Annual Meeting of the American Academy of Allergy, Chicago, Dec. 11, 1945.

‡This investigation was aided by a grant generously given by Mr. Martin Goodman of New York City.

§Personal Communication.

||Made by Kaz Manufacturing Co., 540-12th Ave., N. Y. City.

sure, and a regulating valve which controls the onset and rate of flow of the medication.

Forty adult patients have been treated by the inhalation of aminophyllin aerosol, and the results are reported (Table I), in view of the current interest in the treatment of asthma with aerosols of penicillin and sulfonamides.[7] Some patients were treated with penicillin aerosol alone, or in combination with aminophyllin. The present report, however, concerns itself primarily with aminophyllin aerosol.

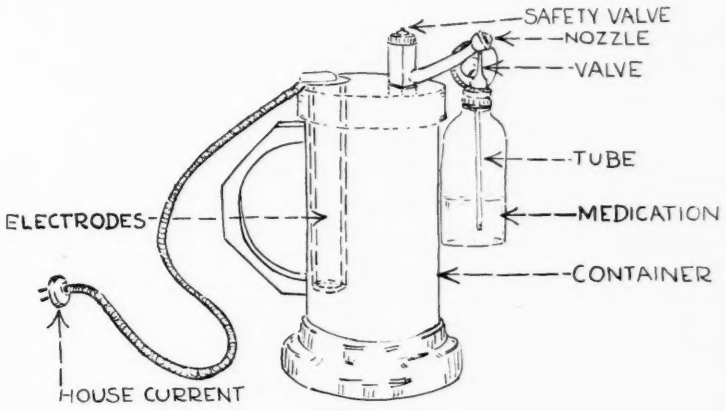

Fig. 1.

In summary, Table I reveals that in the 40 patients treated with aerosol aminophyllin, the ages ranged from fifteen to seventy-two years, and the duration of asthma was from one to fifty years. Thirty-two of these patients (80 per cent) obtained some relief from the inhalation of the aerosol produced from the contents of one or two ampules (10 c.c. or 20 c.c. containing .25 and .5 Gm. aminophyllin, respectively). Where there was a response to this therapy, the patient often reported improvement within a matter of minutes, even before cessation of treatment which lasts ten to fifteen minutes. In some instances, the relief obtained was slight and temporary; in others, it was marked and of long duration. In 5 instances patients responded favorably to aminophyllin aerosol, after failing to respond to aminophyllin intravenously. The converse was also true—some patients unresponsive to inhalation did respond to intravenous therapy. Some were responsive to both, and some to neither.

These favorable results were tempered by complete failures in eight instances (20 per cent), in two of which there were aggravation of symptoms due to intolerance of steam.

VITAL CAPACITY STUDIES

To evaluate aminophyllin aerosol therapy objectively, vital capacity studies of nine patients were done. Subjectively, patients often reported marked relief, after therapy, yet wheezing was still present. The actual increase in vital capacity is a better criterion for improvement; it can be measured and is less apt to be modified by psychogenic factors.

TABLE I. RESULTS OF TREATMENT OF FORTY PATIENTS SUFFERING

CASE NO.	NAME	AGE (YRS.)	SEX	TYPE OF ASTHMA	PULMONARY OR CARDIAC COMPLICATIONS	DURATION OF ILLNESS	DOSE OF AMINO-PHYLLIN BY AEROSOL	SUBJECTIVE RESPONSE
1	C. B.	35	F.	Mixed	Bronchitis	8 yrs.	.25 Gm.	Marked relief
2	A. S.	67	M.	Mixed	Bronchiectasis	22 yrs.	.25 Gm.	Marked relief after second treatment
3	J. B.	19	F.	Mixed	Slight emphysema	17 yrs.	.25 Gm.	Moderate relief at first—later marked
4	D. R.	57	M.	Infective	Emphysema	?	.5 Gm.	Marked relief
5	D. C.	38	M.	Infective	Bronchiectasis	11 yrs.	.25 Gm. and .5 Gm.	No relief to moderate relief
6	M. F.	62	F.	Mixed	Hypertensive cardiovascular disease	20 yrs.	.25 Gm.	Slight relief
7	E. H.	49	F.	Intrinsic	Hypertensive cardiovascular disease, bronchietasis, emphysema	23 yrs.	.25 Gm.	Was worse after treatment
8	A. S.	47	F.	Intrinsic	Slight emphysema	5 yrs.	.25 Gm.	Marked relief
9	B. K.	44	F.	Mixed		7 yrs.	.25 to .5 Gm.	No relief
10	R. P.	31	F.	Mixed	Moderate emphysema	20 yrs.	.25 Gm.	Slight relief, afraid of steam
11	R. A.	59	F.	Intrinsic	Moderate emphysema	8 yrs.	.25 Gm.	Marked relief
12	M. S.	38	F.	Mixed		10 yrs.	.25 Gm. .25 Gm.	Marked relief

FROM ASTHMA, BY INHALATION OF AEROSOL OF AMINOPHYLLIN

CHANGE IN PHYSICAL FINDINGS	CHANGES IN VITAL CAPACITY	TIME OF RESPONSE (MINUTES)	DURATION OF RELIEF	CONTROL INHALATIONS	PREVIOUS TREATMENTS	NO. OF TREATMENTS	COMMENT
Reduction in rales, wheezing and dyspnea	–	10	3 mos.	–	Aminophyllin i.v.	1	Uterine bleeding—unable to operate because of asthma; after one inhalation was able to operate
Less dyspnea and wheezing	–	15	4 hrs.	–	Aminophyllin i.v., epinephrine dust, bacterial vaccine, ragweed. Penicillin intramuscularly—sulfonamide therapy	50 plus	Continuous asthma in spite of all treatment. Excellent response to aminophyllin aerosol—later became refractory
Slight changes at first, later marked reduction in all signs	–	15	4-8 hrs.	–	Aminophyllin i.v., epinephrine, ephedrine	20 plus	Status of five days' duration broken after second treatment
Less dyspnea and wheezing	+15%	5			Epinephrine, aminophyllin i.v., and rectally	1	Continuous asthma 48 hours; unresponsive to intravenous aminophyllin—responsive to aerosol
Varied	See Fig. 3	10-15	0-4 hrs.	See Fig. 3	Epinephrine, aminophyllin i.v., oxygen continuous	20 plus	Severe asthma and bronchiectasis—good response at times to aerosol therapy
Slight reduction in wheezing		15	2 hr.		Ephedrine, aminophyllin, suppositories	1	Poor response
More dyspneic				Worse after steam		4	Aggrevation after each of the treatments
Slight wheezing, less rales		30	No return of symptoms for months		Ephedrine, epinephrine, inhalations	10	Patient in status for a week when admitted. Aminophyllin given b.i.d. prophylactically by inhalation
None					Ephedrine, epinephrine, inhalations	4	No response. Patient died several days later
Breathing easier					Pollen, dust, vaccine	4	Psychoneurotic. Afraid of steam. Could use only between attacks.
Slight improvement		10	2 wks.	Steam gave some relief	Dust, vaccine, amino. supp., ephedrine	1	Slight improvement with steam. Marked when aminophyllin was given.
Marked improvement in dyspnea; still wheezing		15 15	2 weeks Well for months		Ephedrine, amino. supp.	2	Slept for first time in 10 days after treatment

TABLE I

CASE NO.	NAME	AGE (YRS.) SEX	TYPE OF ASTHMA	PULMONARY OR CARDIAC COMPLICATIONS	DURATION OF ILLNESS	DOSE OF AMINOPHYLLIN BY AEROSOL	SUBJECTIVE RESPONSE
13	R. S.	42 F.	Intrinsic	Slight emphysema	2 yrs.	.25 Gm.	Marked relief
14	F. G.	33 F.	Intrinsic	Slight emphysema	12 yrs.	.25 Gm. .25 Gm.	Worse
15	F. E.	60 F.	Intrinsic	Marked emphysema	22 yrs.	.25 Gm.	Moderate relief
16	E. McD.	31 F.	Mixed		6 yrs.	.25 Gm. .25 Gm. .25 Gm.	Marked improvement
17	R. W.	63 M.	Mixed	Cor. pulmonale bronchiectasis, marked clubbing of fingers	50 yrs.	.25 Gm.	Very slight improvement
18	B. Y.	49 F.	Mixed	Emphysema	49 yrs.	.25 Gm.	No relief
19	A. C.	28 F.	Mixed	None	22 yrs.	(a).25 Gm. (b).25 Gm.	(a) No relief in 10 min. (b) Marked relief
20	R. R.	15 M.	Mixed	None	11 yrs.	.25 Gm.	Moderate relief
21	L. S.	34 F.	Mixed	None	5 yrs.	.25 Gm.	Marked relief
22	J. E.	40 F.	Intrinsic	None	10 yrs.	.25 Gm.	Moderate relief
23	S. P.	70 M.	Mixed	Emphysema	15 yrs.	.25 Gm.	Moderate relief
24	J. W.	38 M	Intrinsic	Emphysema	10 yrs.	.25 Gm.	No relief
25	M. G.	66 M.	Intrinsic	Marked emphysema		.25 Gm.	No relief
26	T. C.	62 F.	Intrinsic		1 yr.	.25 Gm. .25 Gm.	Marked relief, Same
27	P. R.	43 F.	Mixed			.25 Gm. .25 Gm.	Marked relief Marked relief
28	S. A.	54 F.	Intrinsic	Hypertensive, emphysema	30 yrs.	.25 Gm.	Marked relief
29	M. C.	31 F.	Mixed		12 yrs.	.25 Gm.	No relief immediately after treatment
30	G. H.	60 F.	Mixed	Emphysema	20 yrs.	.25 Gm.	Marked relief
31	P. Q.	58 F.	Intrinsic	Cor-pulmonale	5 yrs.	.25 Gm. .25 Gm.	Marked relief Marked relief
32	J. C.	72 M.	Intrinsic	Hypertensive arteriosclerotic heart disease	12 yrs.	.5 Gm.	Moderate relief

—CONT'D

CHANGE IN PHYSICAL FINDINGS	CHANGES IN VITAL CAPACITY	TIME OF RESPONSE (MINUTES)	DURATION OF RELIEF	CONTROL INHALATIONS	PREVIOUS TREATMENTS	NO. OF TREATMENTS	COMMENT
Marked improvement in all physical signs		10	No asthma to date		Dust, vaccine, ephedrine	1	Asthma for 2 weeks. After one treatment was improved and is well
				Steam alone made her worse	Dust, vaccine, ephedrine, amino. supp.	2	Steam made her worse
Less wheezing and dyspnea		10	3 hrs.		Dust, vaccine, ephed. amino.	5	Improved less with each subsequent treatment
Disappearance of all signs		5 5 5	36 hrs. 24 hrs. 48 hrs.		Ephedrine, amino. supp.	3	Marked response to inhalation
No change		10	½ hr.		Ephedrine, amino. supp., epinephrine, inhalations	1	Coughed up a great deal of infected sputum with only slight relief
No change						2	No relief
(b) Complete clearance of chest		(b) 30	(b) 4 mo.		Amino. supp., ephedrine, ep. inhalations	2	Marked relief when second dose was given.
Marked improvement	+56.9%	2-5	3-6 days	Steam, no relief	Tedral amino. suppositories	3	Marked improvement in vital capacity
Slight decrease		3	14 days			1	Hyperventilated. Complained of dizziness and tingling in fingers
None		2				1	Good relief with changes Px.
Definite improvement		10	5 hrs.			1	
No change							Pansinusitis, polyposis, intractable asthma
Unchanged					Dust, vaccine, ephedrine	1	Nothing gave him relief in past
Improved	+ 5.7%	5	6 hrs.		Dust, vaccine, ephedrine amytal	2	Second treatment, patient not too comfortable
Improved		5					
Improved		3	5-6 hrs.			2	
Improved							
Chest clear except for rales		8	3 hrs.	Steam, no relief		1	Marked subjective and objective improvement
No change	- 6.5%		2 days		Ragweed, dust, feathers, vaccine	1	Reduction in vital capacity yet relief for 2 days. Slept for first time in 2 weeks
Complete disappearance of all signs		10			Trees, timothy, plantain, dust	1	Marked subjective and objective improvement
Marked reduction in physical findings		15	4-6 hrs.		Aminophyllin i.v.	2	Excellent response in refractory case
Diminished wheezing		15	1 hr.			1	

TABLE I—

CASE NO.	NAME	AGE (YRS.) SEX	TYPE OF ASTHMA	PULMONARY OR CARDIAC COMPLICATIONS	DURATION OF ILLNESS	DOSE OF AMINO-PHYLLIN BY AEROSOL	SUBJECTIVE RESPONSE
33	E. J.	58 M.	Mixed	Emphysema fibrosis	23 yrs.	.5 Gm. .5 Gm.	Slight relief Moderate relief
34	W. S.	63 M.	Intrinsic	Emphysema, arteriosclerotic heart disease	2 yrs.	.5 Gm. .5 Gm.	No relief Slight relief
35	D. G.	50 F.	Intrinsic	Bronchitis for ten years	10 days	.5 Gm.	Slight relief
36	M. S.	63 F.	Intrinsic	Bronchiectasis	47 yrs.	.5 Gm.	Slight relief
37	O. R.	60 M.	Intrinsic	Coronary pulmonale, emphysema	25 yrs.	.5 Gm.	Marked relief
38	W. B.	61 M.	Mixed	Coronary pulmonale, bronchiectasis	6 yrs.	.25 Gm.	Moderate relief
39	A. M.	50 F.	Intrinsic	Bronchitis	15 yrs.	.5 Gm. .5 Gm. 30,000 units Penicillin	No relief Moderate relief
40	E. M.	58 F.	Intrinsic	Possible bronchiectasis, bronchitis	3 yrs.	.5 Gm.	Moderate relief

As will be noted in Fig. 2, eight cases showed improvement in vital capacity ranging from 7.4 per cent to 56.9 per cent. One case showed a decrease of 6.5 per cent within ten minutes after treatment, but was relieved of asthma for two days—for the first time in a week—and asked for further treatment. The 15 per cent increase in the case of Mr. DeC. is the latest increment obtained with aminophyllin, after other measures had already improved his vital capacity by 31.5 per cent, as seen in Fig. 3. The average increase in vital capacity for all nine cases was 20.6 per cent.

A series of vital capacity studies were undertaken with patient Mr. DeC. (Case 5) to evaluate the role of steam, and to eliminate any possible psychogenic factor. For the latter purpose ammonium chloride solution (5 per cent), whose bitter taste resembles that of aminophyllin, was substituted as a control unknown to the patient. As recorded in Fig. 3, there were significant increases with steam (11.8 per cent) and with ammonium chloride (31.5 per cent), and yet an additional improvement in vital capacity of 15 per cent was obtained after the inhalation of aminophyllin aerosol. All readings were taken ten minutes after cessation of each treatment.

Further vital capacity studies were undertaken with nine patients, to evaluate the effect of the steam on the relief of asthmatic symptoms (Table II).

Here is noted improvement in vital capacity, ranging from 1.8 per cent to 11.1 per cent, demonstrable in five patients. Two patients showed no changes,

CONT'D

CHANGE IN PHYSICAL FINDINGS	CHANGES IN VITAL CAPACITY	TIME OF RESPONSE (MINUTES)	DURATION OF RELIEF	CONTROL INHALATIONS	PREVIOUS TREATMENTS	NO. TREATMENTS	COMMENT
Decrease in dyspnea	+18.2%	10 10	15 min. 3 hrs.		Amino. i.v. Supp. KI	2	Definite relief. Improvement in vital capacity
No change reduction in dyspnea		15	1 hr.		Aminophyllin i.v.	2	Vomited after first treatment. Refractory to aminophyllin i.v.
No change except less dyspnea		15		Steam negative	Aminophyllin i.v.	1	Slight relief by aminophyllin i.v. and by inhalation (died)
Less dyspnea	+13.6%	15				1	Improvement in vital capacity
Less dyspnea, less wheezing	+ 7.4%	15	12 hrs.		Benadryl tablets	1	Immediate relief slept first time in 3 nights
Decrease in dyspnea and wheezing	+40.5%	15	12 hrs.		Aminophyllin suppositories	1	Marked increase in vital capacity
Slight decrease in dyspnea	+34.67%	15			Aminophyllin i.v., K.I.	12	Also given penicillin with aminophyllin inhalations with relief.
Decrease in wheezing and dyspnea		15			estrogen		
Wheezing and dyspnea subsided		15			Aminophyllin suppositories, K.I.	20	No asthma while getting inhalation. Penicillin given because of fever. 500,000 units.

and two showed a decrease in vital capacity of 2.1 per cent and 10.2 per cent. The average increase in vital capacity due to steam alone, of all nine cases, was 2.5 per cent—approximately $\frac{1}{10}$ the improvement noted with aerosol of aminophyllin.

To compare the relative efficiency of aminophyllin aerosol with aminophyllin administered intravenously, nine asthmatic patients were treated with 5 c.c. (.125 Gm.) of aminophyllin by intravenous injection. The dose of 5 c.c.

TABLE II. VITAL CAPACITY STUDIES OF NINE PATIENTS TREATED WITH STEAM

PATIENT	VITAL CAPACITY		GAIN OR LOSS	
	BEFORE INHALATION (C.C.)	TEN MINUTES AFTER INHALATION (C.C.)	(C.C.)	PER CENT
Wis.	2350	2300	−50	−2.1
Gol.	1600	1600	0	0
Per.	2700	2750	50	1.8
Nov.	2750	2850	100	3.6
DeC.	1300	1450	150	11.5
Pro.	2150	2300	150	7.
Ghi.	2250	2500	250	11.1
Har.	1900	1900	0	0
Mad.	2450	2200	−250	−10.2
			Total gain	22.7%
			Average gain	2.5%

was decided upon as being a fair equivalent to the 10 c.c. of aminophyllin by inhalation. Actually, considerably less than 5 c.c. is inhaled in the aerosol treatment. There is loss by dissipation into the air (as it is not possible to breathe fast enough to inhale all the aerosol produced), and by condensation on the patient's face. These studies (Table III) with intravenous aminophyllin revealed that the average increase in vital capacity demonstrated by these nine patients was 12 per cent, which is considerably less than that noted with the inhalation method (20.6 per cent).

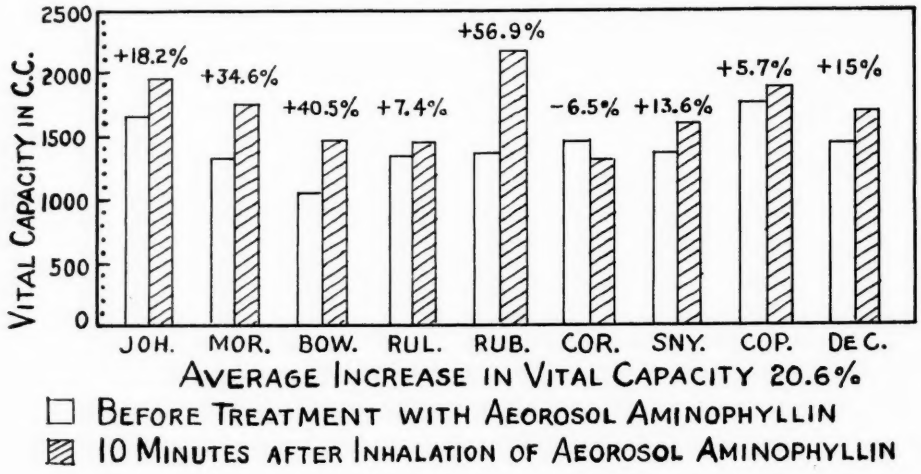

Fig. 2.—Vital capacity studies of nine patients treated with aerosol aminophyllin.

These comparisons are limited in value, in view of the fact that a different set of patients was used for each of these control studies. Ideally, the same patients having the same degree of asthma should have been treated, and this was attempted. It was impossible, however, to meet these conditions, since patients improved and were discharged. Neither could we get the same patient in the same state of asthma as it originally existed. Nevertheless, we feel that these studies definitely indicate that aerosol aminophyllin gave greater improvement than steam alone, or an equivalent of aminophyllin introduced intravenously (Fig. 4).

DISCUSSION

As evidenced by the clinical response of the patient and by the vital capacity studies, there is no doubt that aminophyllin aerosol when inhaled is effective in the treatment of asthma. Possibly, some improvement is due to the liquefying action of steam on the sputum, in accordance with the report of Basch, Hollinger, and Poncher.[8] That this does not hold here entirely is evidenced by the control studies with steam as observed in nine patients (Table I), and in the case of Mr. DeC. (Fig. 3).

We must, therefore, explain the improvement evidenced by these patients as being largely due to the aminophyllin. From the work of Young and Gilbert[9] we conclude that the results obtained were due to the antispasmodic

action of aminophyllin on the bronchial masculature. This effect is not mediated through central (nervous) action, but is a direct effect on the muscle itself, since an isolated segment responds to the dilating effect of aminophyllin.

More remarkable is the dosage required to produce the results. Of the 10 c.c. of aerosol containing .25 Gm., only very little is actually inhaled by the patient employing this open method. Considerable amounts of the aerosol are lost into the atmosphere. Some is condensed on the patient's face and in the patient's mouth, and is swallowed or expectorated. We can only guess that, at the most, one-fifth of the aerosol is inhaled—the actual dose, therefore, being .05 Gm.—an amount which we ordinarily hold ineffective when given intravenously.

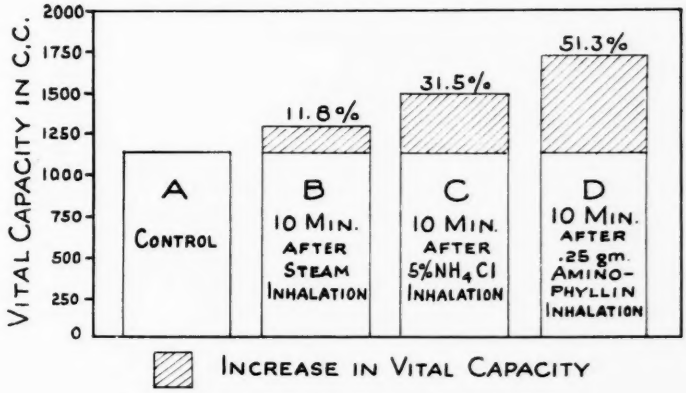

Fig. 3.—Vital capacity studies in Case DeC.

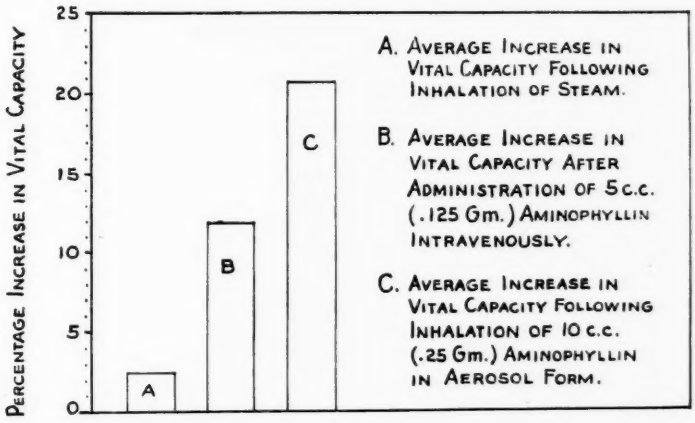
PERCENTAGE INCREASE IN VITAL CAPACITY
25
20
15
10
5
0
A
B
C
A. AVERAGE INCREASE IN VITAL CAPACITY FOLLOWING INHALATION OF STEAM.
B. AVERAGE INCREASE IN VITAL CAPACITY AFTER ADMINISTRATION OF 5 c.c. (.125 Gm.) AMINOPHYLLIN INTRAVENOUSLY.
C. AVERAGE INCREASE IN VITAL CAPACITY FOLLOWING INHALATION OF 10 c.c. (.25 Gm.) AMINOPHYLLIN IN AEROSOL FORM.

Fig. 4.—Comparison of increase of vital capacity obtained by inhalation of steam, aminophyllin aerosol, and by the intravenous administration of aminophyllin.

The following procedure in the treatment of asthma with aerosol of aminophyllin is now recommended: the contents of one ampule (.25 Gm. in 10 c.c.) is aerosolized, and if there is no relief in fifteen minutes after cessation of treatment, the same dosage is repeated. In most instances, relief is obtained within a few minutes of exposure to the aerosol.

TABLE III. VITAL CAPACITY STUDIES OF NINE PATIENTS TREATED WITH .125 GM. AMINOPHYLLIN INTRAVENOUSLY

PATIENT	VITAL CAPACITY		GAIN OR LOSS	
	BEFORE INJECTION (C.C.)	TEN MINUTES AFTER INJECTION (C.C.)	(C.C.)	PER CENT
E. J.	2100	2500	400	19
S. C.	2300	2650	350	15.2
H. V.	2000	2150	150	7.5
G. B.	2750	2700	-50	-1.8
T. C.	2200	2450	250	11.3
D. E.	2350	2600	250	10.6
D. C.	1500	1800	300	20.0
J. B.	2250	2600	350	15.6
L. D.	2300	2550	250	10.9
			Total Gain	108.3%
			Average Gain	12.03%

Where there is an associated bronchitis or bronchiectasis, penicillin in aerosol form is also given, using the same device (the penicillin is unaffected by steam).[5] It is best to give the penicillin after the aminophyllin has exerted its effect. The increase in vital capacity permits a greater inhalation of the penicillin, and enhances its effect. The recommended dosage of penicillin is 20 to 30,000 units every three hours.

Utilizing the same apparatus, it is also possible to use mixed aerosols of aminophyllin and penicillin, or combinations of these with sodium sulfadiazine (5 per cent). In view of the experience with patient DeC. (Fig. 3), we occasionally use ammonium chloride (10 c.c. of 5 per cent solution) along with the aminophyllin, and believe this combination to be very effective. These observations will be reported later.

It should be noted that the steam, emerging in this device from a very small aperture, is quickly cooled in its sudden expansion. There is no danger of injury to the respiratory tract from such inhalations, according to the experimental studies of Moritz, Henriqes, and McLean.[10]

Preliminary observations by Prigal and Speer with sulfadiazine and penicillin aerosols showed rapid absorption of these aerosols via the lungs, and maintenance of high blood levels over a period of several hours. This possibly indicates retention of these aerosols, either in the capillaries or in the alveoli of the lung until absorbed. This may hold true for the aminophyllin aerosol as well.

The remarkable rapidity with which an aerosol is absorbed is due to the tremendous surface of lung tissue available for such absorption. It is estimated that there are about 300,000,000 alveoli, each one lined by capillaries whose wall is 1/30,000 of an inch thick, the thinnest in the body. This provides a surface of 700 square feet for absorption.[11]

None of the usual complaints noted with the administration of aminophyllin intravenously, such as syncope, nausea, or vomiting, were noted following aminophyllin aerosol, nor have we encountered any deaths such as have been attributed to aminophyllin.[12] One patient hyperventilated and complained of lightheadedness, with numbness and tingling of the fingers. This was readily over-

come by making the patient hold her breath. Another patient had slight burning retrosternally on one occasion, but continued further treatment without complaint. Still another had temporary smarting of the eyes.

Barach[13] has emphasized the value of aminophyllin in controlling the asthmatic seizure by continuous bronchial relaxation. This can be effected efficiently and economically through the use of the aerosolizer employed in this study. The apparatus is inexpensive. Furthermore, the patient can be taught to administer his own aminophyllin aerosol treatment, so that he can avoid many hours of suffering while waiting for a physician. The difficulties which accompany intravenous medications are also eliminated.

SUMMARY

1. Forty adults suffering from bronchial asthma were treated by inhalations of an aerosol of aminophyllin produced by a new device—a combined steam generator and aerosolizer.

2. Thirty-two patients (80 per cent) were afforded some relief, ranging from slight temporary relief to marked and prolonged relief.

3. Five cases (12.5 per cent) of severe asthma responded to aminophyllin by inhalation, after failing to respond to aminophyllin intravenously. Some cases unresponsive to the aerosol did respond to the intravenous injection. Some cases responded to neither method.

4. Vital capacity studies of nine asthmatic patients, before and after the administration of aminophyllin aerosol, showed an average increase of 20.6 per cent. This compares favorably with a recorded improvement in vital capacity of 12 per cent, obtained by the intravenous administration of 5 c.c. (.125 Gm.) of aminophyllin.

5. The steam generated by the aerosolizer may, in some instances, on inhalation, afford some relief (five out of nine patients responded favorably), but this is slight when compared with the relief obtained with aminophyllin either by inhalation or by intravenous administration.

6. Utilizing the same apparatus, aerosol of penicillin was administered in conjunction with or following an aminophyllin inhalation treatment, where there was evidence of respiratory infection.

7. The aerosolizer used in this investigation is inexpensive, and the patient easily learns to use it for the self-administration of aminophyllin or penicillin.

The authors wish to express thanks to Dr. Abner M. Fuchs for permission to treat his patients on the allergy service of Metropolitan Hospital.

REFERENCES

1. Hermann, G., and Aynesworth, M. B.: Successful Treatment of Persistent Extreme Dyspnoea—"Status Asthmaticus." Use of Theophylline Ethylene Diamine (Aminophyllin) Intravenously, J. Lab. & Clin. Med. **23**: 135, 1937.
2. Prigal, S. J., Schulman, P., and Fuchs, A. M.: The Treatment of Asthma With Rectal Suppositories of Aminophyllin and Sodium Pentobarbital, J. Allergy **17**: 172, 1946.
3. Segal, M. S.: Advances in Inhalation Therapy, With Particular References to Cardiorespiratory Disease, New Eng. J. Med. **231**: 553, 1944.
4. Richards, D. W., Barach, A. L., and Cromwell, H. A.: Uses of Vaporized Bronchodilator Solutions in Asthma and Emphysema: A Continuous Inhalation Method for Severe Asthmatic States, Am. J. Med. Sc. **199**: 225, 1940.

5. Prigal, S. J., and Speer, F. D.: A New Method of Aerosolization of Penicillin, Sulfonamides, and Other Medications for Inhalation Therapy, Bull. New York Med. Coll. **8**: 21, 1945.
6. Prigal, S. J.: The Production of Aerosols From Medicated Solutions; a Combined Steam Generator and Aerosolizer, J. A. M. A. **131**: 398, 1946.
7. (a) Barach, A. L., et. al.: Inhalation of Penicillin Aerosol in Patients With Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess, Ann. Int. Med. **22**: 485, 1945.
   (b) Hampton, S. F., Wein, M. B., Allen, W., Thompson, C. G., and Starr, M. P.: The Clinical Use of Penicillin in the Treatment of Intrinsic Bronchial Asthma, J. A. M. A. **127**: 1108, 1945.
   (c) Applebaum, I. L.: The Treatment of Bronchial Lesions by Inhalation of Nebulized Solutions of Sodium Sulfathiazole, Dis. of Chest **10**: 415, 1944.
8. Basch, F. P., Hollinger, P., and Poncher, H. G.: Physical and Chemical Properties of Sputum: Influence of Drugs, Steam, Carbon Dioxide and Oxygen, Am. J. Dis. Child. **62**: 1149, 1941.
9. Young, H. R., and Gilbert, R. P.: The Use of Theophyllin With Ethylenediamine (Aminophyllin) for the Control of Bronchial Spasm, J. Allergy **12**: 235, 1941.
10. Moritz, A. R., Henriqes, F. C., Jr., and McLean, R.: The Effects of Inhaled Heat on the Air Passages and Lungs. An Experimental Investigation, Am. J. Path. **21**: 311, 1945.
11. Harvey, B. C. H.: Simple Lessons in Anatomy, Am. Med. Assn. 1932, pp. 242-5.
12. Merrill, G. A.: Aminophyllin Deaths, J. A. M. A. **123**: 115, 1943.
13. Barach, A. L.: Rectal Instillation of Aminophyllin in Intractable Asthma, Ann. Int. Med. **22**: 485, 1945.

55 Park Avenue.

INFLUENCE OF SOYBEAN PRODUCTS ON THE IODINE NUMBER OF THE PLASMA LIPIDS AND THE COURSE OF ECZEMA*†

ALBERT V. STOESSER, M.D., PH.D., MINNEAPOLIS, MINN.

BURR and Burr[1] stated that rats placed on fat-free diets which were adequate in all other respects first developed scaliness of the skin and then necrosis of the tail. The next year Burr[2] reported that when fats containing unsaturated fatty acids such as linoleic and linolenic were added to the diets of these animals, their skin scaliness disappeared. Later, Hansen[3, 4] observed that the degree of unsaturation of the fatty acids in the blood as measured by the level of iodine absorption was lower than normal, not only in Burr's rats suffering from fat deficiency, but also in infants with eczema. The ingestion of raw linseed oil, corn oil, and lard revealed that fats with a relatively high unsaturated fatty acid content could raise the iodine absorption values of the plasma lipids of these young children.

Eczema of infancy is often due to cow's milk sensitivity, and soybean preparations have been used as a substitute. A clinical evaluation[5] of one of these products showed that when external care of the skin is of the best, and a good elimination diet is employed, soybean milk can be of additional benefit.

The present study deals with changes in iodine numbers of the total fatty acids of the plasma lipids in milk-sensitive infants who were fed daily 900 to 1,200 Gm. of a soybean food,‡ which contained 4 per cent soybean oil with an iodine absorption value ranging from 119 to 135. Seventeen patients from 3 to 14 months of age were chosen, and divided into two groups. Eleven were acutely ill with erythema and papules, oozing and crusting confined chiefly to the cheeks, but spreading to the forehead and scalp or ears and neck. Six had less of the exudative characteristics, there being redness, thickening, induration, and scaliness of the skin, with marked itching and a tendency to spread to the trunk and extremities.

Before the study was begun all of the children had been receiving diets consisting of an adequate caloric intake. Mixtures of cow's milk and water with low iodine absorption values were employed. The older infants also received cereals, meats, vegetables, and fruits. None of the patients had been given eggs. Sensitivity to cow's milk was determined by trial diet or cutaneous testing. Before the soybean preparation was used, a blood sample was collected. After three weeks' ingestion of the product, the second specimen was drawn, to be followed by others obtained at approximately three-week intervals. All blood samples were taken uniformly after a fast of fourteen hours. The total fatty acids were obtained by the microgravimetric method

Presented at the Second Annual Meeting of the American Academy of Allergy, Chicago, Illinois, December 10, 1945.

*From the Division of Pediatrics of the Minneapolis General Hospital, and the Department of Pediatrics of the University of Minnesota Medical School.

†Aided by grants from Medical Research Fund of Graduate School of University of Minnesota, and from the Borden Company.

‡Mull-Soy prepared and furnished by the Prescription Products Division of the Borden Company.

of Wilson and Hansen.[6] Hansen's[7] modification was followed to determine the iodine absorption of the serum fatty acids.

The results are summarized in Table I.

The infants with the more severe skin changes had iodine numbers averaging 71, which is much below normal. However, after three or more weeks of ingestion of the soybean milk, the values rose until an average of 118 was reached which is within the normal range. This situation was associated with a favorable response to external therapy.

TABLE I. IODINE NUMBERS OF THE TOTAL FATTY ACIDS OF THE PLASMA LIPIDS BEFORE AND DURING THE INGESTION OF A SOYBEAN FOOD

GROUP I. INFANTS WITH LOCALIZED WEEPING ECZEMA					GROUP II. INFANTS WITH WIDESPREAD INDURATED ECZEMA				
CASE NO.	A*	B	C	D	CASE NO.	A*	B	C	D
1	58	65	85	100	1	85	133	90	120
2	78	87	118	125	2	100	104	103	120
3	60	70	97	107	3	90	115	115	105
4	80	93	127	137	4	105	100	120	88
5	67	80	110	120	5	97	108	104	120
6	82	105	--	--	6	115	95	108	98
7	70	83	112	122					
8	83	112	132	--					
9	75	85	115	--					
10	85	113	135	--					
11	95	118	--	--					
Average	71	91	103	118	Average	98	109	106	108

*A—Blood sample collected before the soybean food was started.
B—Blood sample collected about three weeks after ingestion of the food.
C—Blood sample collected after six weeks of ingestion of the food.
D—Blood sample collected after nine weeks of ingestion of the food.

The other group of children with moderate but widespread skin manifestations had little change in the iodine numbers of the total serum fatty acids. The ingestion of the soybean preparation produced no consistent result, the initial average iodine absorption values moving up from 98 after some fluctuation to only 108. The response to other forms of therapy was not uniform.

The results reveal that there is some correlation between the level of the unsaturated fatty acids of the plasma lipids and the type and course of infantile eczema. They also confirm the observations presented in a previous communication[8] in which it was noted that during acute infections of the respiratory tract in infants with eczema, the skin showed temporary improvement at the onset of fever, but was much worse thereafter. This may be due to the fact that early in an acute infection there is a sudden flood of unsaturated fatty acids into the blood stream to be followed by a fall to abnormally low levels.[9, 10]

This is the first of a series of communications which will represent investigations completed and in progress concerning the influence of increasing the iodine number of the plasma lipids in some cases of eczema on the response to routine therapy. More work must be done to obtain a better classification of the eczemas and to find the most practical method of boosting the unsaturated fatty acids of the plasma lipids when they are found low.

REFERENCES

1. Burr, G. O., and Burr, M. M.: A New Deficiency Disease Produced by Rigid Exclusion of Fat from Diet, J. Biol. Chem. **82**: 345, 1929.
2. Burr, G. O.: On the Nature and Role of the Fatty Acids Essential in Nutrition, J. Biol. Chem. **86**: 587, 1930.
3. Hansen, A. E., and Burr, G. O.: Iodine Numbers of Serum Lipids in Rats Fed on Fat-Free Diets, Proc. Soc. Exper. Biol. & Med. **30**: 1200, 1933.
4. Hansen, Arild E.: Serum Lipid Changes and Therapeutic Effects of Various Oils in Infantile Eczema, Proc. Soc. Exper. Biol. & Med. **31**: 160, 1933.
5. Stoesser, A. V.: Clinical Evaluation of Soy Bean Food in Eczema of the Child, Ann. Allergy **2**: 404, 1944.
6. Wilson, W. R., and Hansen, A. E.: Study of the Serum Lipids by a Microgravimetric Technique, J. Biol. Chem. **112**: 457, 1936.
7. Hansen, Arild E.: Nature of Fatty Acids of Acetone Insoluble (Phospholipid) Fraction of Serum, Proc. Soc. Exper. Biol. & Med. **40**: 376, 1939.
8. Stoesser, A. V.: Influence of Acute Infections on the Plasma Lipids and the Course of Eczema, J. ALLERGY **13**: 248, 1942.
9. Boyd, E. M.: The Lipopenia of Fever, Canad. M. A. J. **32**: 500, 1935.
10. Stoesser, A. V.: Iodine Number of Serum Fatty Acids in Acute Infections of Infants With and Without Eczema, Proc. Soc. Exper. Biol. & Med. **34**: 12, 1936.

Original Articles

THE EFFECT OF BETA-DIMETHYLAMINOETHYL-BENZHYDRYL-ETHER-HYDROCHLORIDE ON THE HISTAMINE THRESHOLD OF HUMAN SKIN*

MILTON B. COHEN, M.D., HAROLD J. FRIEDMAN, M.D., JONATHAN ZONIS, M.D., MEADE BURKE, M.D., AND LEWIS E. ABRAM, M.D., CLEVELAND, OHIO

DURING the past year Loew and his associates[1, 2] have reported that beta-dimethylaminoethyl-benzhydryl-ether-hydrochloride is effective against anaphylactic shock in guinea pigs and in preventing fatal "asthma" induced by the inhalation of histamine. This preparation is at least 30 times as effective as theophylline-ethylene diamine as a bronchodilator, and is about twice as effective as N-phenyl-N-ethyl-N′-diethylethylene diamine, the best of the Forneau histamine antagonists. Like the Forneau preparations, this substance diminishes the blood pressure-depressing effect of histamine and, therefore, seems to have an effect on the vascular musculature as well as on that of the bronchi.

We obtained a supply of this material† (Benadryl) to test its effects in patients with allergic conditions. Our initial experiences showed it to be effective in the control of about 80 per cent of the cases of chronic urticaria after oral administration. Since the lesion in urticaria is a vascular phenomenon, it seemed obvious that the oral administration of this substance diminished the local capillary reactivity to H-substance.

We have reported studies[3] on the skin test threshold to histamine and eserine in normal man and in man immunized against histamine by means of histamine-azo-protein. We now wish to report similar studies on the effect of this drug.

In discussing the results of our previous studies with various observers, we have been told that they had difficulty in determining differences in the zone of effectiveness due to inability to standardize their techniques. Most of them attempted to use the size of the wheal induced by histamine as their standard of comparison. In our experience this cannot be done satisfactorily. It is necessary to determine the smallest amount of histamine which can produce the first evidence of a wheal. Because of this confusion, and since our method has never been described in detail, we shall review it.

METHOD

Histamine dilutions are made in buffered saline pH 7.0 from tablets of histamine acid phosphate containing the equivalent of 1 mg. of histamine base. Fresh solutions and dilutions are made for each series of tests and are discarded

*From the Asthma and Hay Fever Clinic.

†Through the kindness of Dr. E. A. Sharpe of Parke Davis and Company.

after four hours. The tests are performed by iontophoresis, since by this method there is little nonspecific irritation of the skin and no significant variation in the amount of the test substance which enters the skin. This is made possible by the use of a nonirritating current of standard amount, an electrode of standard size, and a standard time. The only variable is the strength of the test solution. The apparatus consists of a 45 volt B battery connected in series with a rheostat and a sensitive ammeter. The negative electrode is a piece of lead wrapped with gauze. The positive electrode is made of copper and has a surface of 1 sq. cm. The handle is well insulated. The inner aspect of the forearm is used for testing. It is important to use areas which are free from hair or to shave the areas used for testing. Pieces of filter paper cut to the exact size of the positive electrode are used to carry the test solution. A piece of filter paper is saturated with the solution to be used, the positive electrode is placed on it, and any excess fluid is removed by blotting around the electrode with filter paper. The negative electrode, well wet with tap water, is held firmly in the hand and the current is turned on. We use a current of 1 milliampere, a time of three minutes. At the end of three minutes the positive electrode is removed, washed well in water, and dried. It is then ready for the next test. The treated site is watched for ten to fifteen minutes to note the reaction.

The initial or threshold reaction consists of numerous punctate wheals in the area occupied by the positive electrode. The speed of its development depends on the amount of pressure which has been applied through the electrode. In our experience variations in pressure do not affect the end point, but only the speed of development of the wheal.

In carrying out the threshold test we use dilutions of histamine representing histamine base in amounts varying from 1:200,000 to 1:6,400,000, and physiologic saline as a control.

In work previously reported[3] we showed that in 50 normals tested by this technique the threshold to histamine was 1:6,400,000 in 45 and 1:3,200,000 in five.

When, following treatment with any anti-histamine substance it requires a dilution of 1:1,600,000 or more to produce the initial wheal, we consider the change to be significant.

EXPERIMENTAL STUDY

We administered beta-dimethylaminoethyl-benzhydryl-ether-hydrochloride orally in 50 mg. capsules 4 times daily to a series of patients. The initial cutaneous threshold to histamine was determined before the drug was administered, and after it had been taken for from twenty-four hours to one week. The following chart shows the results, in 20 such patients:

These experiments demonstrate conclusively that there is a well-marked cutaneous anti-histamine effect after the oral administration of this benadryl alkamine ether.

TABLE I. SKIN THRESHOLDS TO DILUTIONS OF HISTAMINE BEFORE AND AFTER TREATMENT

CASE	BEFORE TREATMENT	AFTER TREATMENT	ORDER OF PROTECTION
1	1:6,400,000	1:800,000	8
2	1:6,400,000	1:800,000	8
3	1:6,400,000	1:1,600,000	4
4	1:6,400,000	1:3,200,000	2
5	1:6,400,000	1:800,000	8
6	1:6,400,000	1:1,600,000	4
7	1:6,400,000	1:800,000	8
8	1:3,200,000	1:800,000	4
9	1:6,400,000	1:3,200,000	2
10	1:3,200,000	1:800,000	4
11	1:6,400,000	1:800,000	8
12	1:6,400,000	1:200,000	32
13	1:6,400,000	1:800,000	8
14	1:6,400,000	1:800,000	8
15	Dermatographic	1:400,000	16+
16	Dermatographic	1:1,600,000	4+
17	1:3,200,000	1:400,000	8
18	1:6,400,000	1:400,000	16
19	1:6,400,000	1:800,000	8
20	1:6,400,000	1:800,000	8

TABLE II. THE EFFECT OF AN ORAL DOSE OF 50 MG. ON THE HISTAMINE THRESHOLD

CASE	BEFORE	30 MIN.	2½ HRS.	3½ HRS.
1	1:6,400,000		1:800,000	1:800,000
2	1:3,200,000	1:1,600,000	1:1,600,000	1:800,000

Further studies were carried out to determine the speed of action of the drug. After the initial threshold was determined, a 50 mg. dose was administered orally and tests were made in 30 minutes, 2½ hours and 3½ hours (Table II).

One asthmatic patient in an acute attack was given 8 mg. intravenously in five minutes. The attack was controlled completely. Forty-five minutes later the histamine threshold was 1:200,000. Additional experiments were performed in which areas of normal skin were tested with (1) histamine, (2) mixtures of histamine and the drug, (3) the drug alone. The drug was first implanted in area 1. Area 2 was tested with the mixture and area 3 with histamine alone. Ten minutes after the original testing in area 1, the area was retested with the histamine solution. The results are shown in Table III.

TABLE III

AREA 1		AREA 2	AREA 3	AREA 4
CASE	DRUG	DRUG & HISTAMINE 1:1,600,000	HISTAMINE 1:1,600,000	RETEST OF DRUG AREA WITH HIST. 1-600,000
1	0	slight whealing	confluent wheal	0
2	0	slight whealing	confluent wheal	0
3	0	slight whealing	confluent wheal	0
		DRUG & HISTAMINE 1:800,000		RETEST WITH HIST. 1:800,000
4	0	slight whealing	confluent wheal	0
5	0	slight whealing	confluent wheal	0
6	0	slight whealing	confluent wheal	0

These experiments demonstrate that there is a well-marked definite general cutaneous anti-histamine effect after the oral administration of the benadryl-alkamine-ether and that the effect takes place rapidly. In the amounts of the drug which we have given there is a limit to the anti-histamine effect, since in each patient a wheal can be obtained if sufficient histamine is used.

Even in experiments such as shown in Table III, a reaction can be obtained in the area previously treated with the drug by using increased strengths of histamine. These findings indicate that there is a definite limit to the effectiveness of the drug.

Since the effect of the drug seems to be on the cells of the capillary wall it seems probable that it combines with some of the same active chemical groups with which histamine combines. When these groups are combined with those of the drug they are no longer free to combine with histamine and no reaction occurs. When both the drug and histamine are given simultaneously there is competition for the cells' active chemical groups and some of each substance is combined with the cell. The fact that areas containing the drug will react with stronger histamine solutions can probably be explained by the laws of mass action which apply to many reactions. The drug and histamine compete for the opportunity to attach themselves to the cells and there is a quantitative relationship between them which determines the capacity of each to do so. It seems probable that histamine can displace the drug which has been combined with the tissue cells as its concentration increases.

REFERENCES

1. Loew, E. R., Kaiser, M. E., and Moore, V.: Synthetic Benzhydryl Alkamine Ethers Effective in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine, J. Pharmacol. & Exper. Therap. 83: 120, 1945.
2. Loew, E. R., and Kaiser, M. E.: Alleviation of Anaphylactic Shock in Guinea Pigs With Synthetic Benzhydryl Alkamine Ethers, Proc. Soc. Exper. Biol. & Med. 58: 236, 1945.
3. Cohen, M. B., and Freedman, H. J.: Immunity Against H. Substance, J. Allergy 15: 245, 1944.

THE PREDICTION OF CONSTITUTIONAL REACTIONS BY TESTING WITH RAGWEED POLLEN FRACTIONS*

JONATHAN ZONIS, M.D., BOSTON, MASS., AND NATHAN RUBIN, M.D., CANTON, OHIO

IN 1942 Sherman and Hebald[1] reported a method of foretelling constitutional reactions in ragweed-sensitive patients by skin testing with two fractions made from ragweed pollen. These fractions were prepared from aqueous extracts of short ragweed pollen by precipitation with solutions of ammonium sulfate in accordance with the method of Stull, Sherman, and Hampton.[2] The first fraction, designated by them as Fraction 1, represented the portion of the ragweed extract which precipitated between 0 and 50 per cent saturation with ammonium sulfate; and the second fraction, designated as Fraction 2, represented the portion precipitated between 50 and 100 per cent saturation with ammonium sulfate at pH 4.

Sherman and Hebald tested 221 patients intradermally with these ragweed fractions, and classified them into three groups: (1) those in which Fraction 1 gave a larger reaction than Fraction 2, (2) those in which reactions to the two fractions were equal, and (3) those in which Fraction 2 gave larger reactions than Fraction 1. They used strengths of 1, 10, and 100 protein nitrogen units for the tests. In Group 1 they found 14 per cent (13 of 93) who had constitutional reactions; in Group 2, 75 per cent (81 of 108); and in Group 3, 80 per cent (16 of 20) who had constitutional reactions. They concluded that testing with the two ragweed fractions would "help determine in advance which cases are more apt to have constitutional reactions and should be treated with special caution."

In 1944, Cooke[3] stated: "Patients very sensitive to Fraction 2 do not tolerate large doses of ragweed well, and the intradermal test with the proteose substance called Fraction 2 by Stull will help in advance to determine those problem cases that are apt to have constitutional reactions and should be treated with special caution." In the same manuscript he mentions six cases that reacted to Fraction 1 and not to Fraction 2.

Since systemic reactions constitute serious complications during ragweed therapy, and since no reports of further testing with such fractions have been recorded, we undertook to evaluate the procedure.

Accordingly, we prepared two fractions from short ragweed extract, the first one being the precipitate from 0 to 50 per cent saturation with ammonium sulfate, and the second one the precipitate from 50 to 68 per cent saturation with ammonium sulfate. The precipitations were carried out at 1° C. and pH 4. The material to be precipitated was placed in a cellophane bag and immersed in a jar containing sufficient saturated solution of ammonium sulfate to bring the final concentration to 50 per cent or 68 per cent, depending on the

The expenses of this investigation were defrayed in part by a grant from Parke-Davis and Company.

*From the Asthma and Hay Fever Clinic, Cleveland, Ohio.

final concentration desired. The bag was turned at a constant rate during the dialysis. When equilibrium was established the precipitate was centrifuged off, redissolved in distilled water, and reprecipitated at pH 4. The precipitates were dissolved in distilled water, dialyzed free from sulfate, and made isotonic with sodium chloride. The 68 per cent fraction, according to Stull[4] is the active portion of Fraction 2, and is equal in its nitrogen content but not in its other chemical properties to the first fractions. It is the proteose referred to by Cooke.

With these fractions we tested two groups of patients: (1) 25 who had systemic reactions to ragweed during therapy, and (2) 25 who had none. The tests were done intradermally in duplicate sites with dilutions of 10,100, and 1,000 protein nitrogen units the stronger dilutions being used on the patients who gave mild reactions to their original tests with whole ragweed, and vice versa in the case of the weaker solutions. Thus 35 patients were tested with the 1,000 unit strength, seven with the 100 unit strength, and eight with the 10 unit strength.

RESULTS

Of the 25 cases that had constitutional reactions from ragweed, 15 had skin reactions greater to the second fraction than to the first fraction, eight had equal reactions to both fractions, and two had skin reactions greater to the first than to the second fraction. Of the 25 cases without constitutional susceptibilities, 11 showed larger skin tests to the second than to the first, while 13 had reactions of equal degree, and one had a greater reaction to the first than to the second. No case in the two groups reacted to one fraction alone.

By labeling the first fraction R1 and the second R2, the results are shown diagrammatically in Table I.

TABLE I

	R2 > R1	R1 = R2	R1 > R2
Twenty-five cases with constitutional reactions	15	8	2
Twenty-five cases without constitutional reactions	11	13	1

DISCUSSION AND CONCLUSIONS

Since our figures show no significant disproportion between the two groups of patients, and since none of our patients reacted to one fraction alone, we are forced to conclude that in our hands these ragweed fractions were of no value in determining a possible constitutional reaction in a ragweed sensitive patient during therapy. Our results are best explained on the basis that ragweed fractions are not pure chemical substances, as pointed out repeatedly by Cooke and others. We believe that our fractions are as nearly pure as can he obtained by fractionation with ammonium sulfate. If there were two distinct immunologic fractions, and each contained slight amounts of the other, we should see greater differences in reaction to them when they are diluted to equivalent unit strengths, provided the active material comes down proportionately with phosphotungstic acid precipitable nitrogen. If one should use

as the second fraction all the material precipitated between 50 and 100 per cent saturation of ammonium sulfate instead of that precipitated between 50 and 68 per cent, the same argument holds. These conclusions, although disappointing, are not surprising, since Newell's[5] comprehensive studies (five) of ragweed fractions led to similar deductions as to their impurities. He used the iontophoretic method to test ragweed pollen fractions made with potassium phosphate, ethyl alcohol in various strengths, and ammonium sulfate in one-half and full saturation, and ended his report in 1943 with the statement: "Up to the present none of the fractions prepared by any chemical means even approach the criterion of a pure substance."

REFERENCES

1. Sherman, W. B., and Hebald, S.: A Method of Determining the Probability of Constitutional Reactions During Treatment of Ragweed Hay Fever Patient, Am. J. M. Sc. 203: 383, 1942.
2. Stull, A., Sherman, W. B., and Hampton, S. F.: Separation of Two Antigenic Fractions from Low Ragweed Pollen, J. ALLERGY 12: 117, 1941.
3. Cooke, R.: A Consideration of Some Allergy Problems. II. Serologic Studies of the Skin-Reacting Allergies (Hay Fever); J. ALLERGY 15: 212, 1944.
4. Stull, A.: Importance of Certain Antigenic Fractions of Ragweed Pollen in Relation to Constitutional Reactions During Treatment—Discussion by Stull, J. ALLERGY 12: 606, 1941.
5. Newell, J. M.: Electrophoretic Studies on the Chemical Fractionation of Ragweed Pollen Extracts, J. ALLERGY 14: 444, 1943.

LOEFFLER'S SYNDROME

Report of Two Cases, One With Recurrent Features, and One Associated With Hay Fever

Isadore M. Alpher, M.D., Washington, D. C.

IN THE fourteen years since Loeffler's original report[1] on this syndrome, quite a number of articles (chiefly European) have appeared on the subject. Most of these have concerned themselves with case reports and have added little to Loeffler's concept of the disease. Since its course is benign, there has been little opportunity to report on its pathology. A recent article by Meyenburg,[2] however, describes pathologic pictures which fit closely the probable changes in this syndrome.

That this condition is allergic in origin is agreed upon by most observers. As with other allergic entities, it seems logical to divide the variety of etiologic factors listed in the literature into two general classes. Thus, the cases associated with plant pollen, such as privet[3] and "Maiglöckchen,"[4] and agents such as sulfonamides,[5] belong in the extrinsic group. The intrinsic group (associated with infection) is much more comprehensive and includes tuberculosis,[6] brucellosis,[7] amebiasis,[8] and infection with *Ascaris lumbricoides,*[9] *Necator americanus,*[10] *Fasciola hepatica,*[11] and *Ancylostoma braziliense* (cutaneous helminthiasis).[12]

It is felt that the shock organ in Loeffler's syndrome is the interstitial tissue of the lung rather than the bronchi—as in asthma. (The latter is said to be rare during the acute phase of this syndrome.) Loeffler[1] felt that the lesion was similar to erythema nodosum—that it was a "microbid"—frequently a tuberculid. Braeuning[13] postulated an angioneurotic edema of the lung. Meyenburg[2] called it essentially an "eosinophilic pneumonia." The occurrence of foci of eosinophilic infiltration in organs other than the lungs would seem to postulate a hematogenous pathway for the intrinsic type. There is also the possibility that Loeffler's syndrome may be due to a virus infection in an essentially allergic person.

Meyenburg[2] recently reported the pathologic findings in the cases of four persons dying by accident and who had not complained of illness prior to death. He found an unusual type of lung lesion which seemed to him to correspond to the known phenomena in Loeffler's syndrome. The common findings were hyperemia and a serofibrino-cellular exudate in the lung alveoli rich in eosinophiles (as much as 70 to 80 per cent), as well as eosinophilic infiltration of the interstitial tissue. In one case there was an eosinophilic bronchiolitis only in the pneumonic foci. In another, all bronchioles, even in the lesions, were entirely normal. In two cases he found increased numbers of eosinophiles in other organs, such as the spleen and bone marrow, and, in one case, sections of the liver showed a few foci of eosinophile aggregation with occasional Charcot-Leyden crystals. He was unable to ascribe these lesions to any etiologic factor.

Nagel[14] reported the examination of pleural fluid in a case of Loeffler's syndrome. It was cloudy, yellow, specific gravity 1.020, and congealed on standing. It was very rich in cells of which 83 per cent were eosinophiles (a coincident blood eosinophile count was 9 per cent) and contained many Charcot-Leyden crystals, which he felt were crystallization products of eosinophiles. Although other authors had reported an extraordinary toxicity of such an exudate, he was unable to confirm this.

In most of the cases reported to date, the discussion of the differential diagnostic problem is usually limited to those diseases which are known to be associated with eosinophiles. It seems that only two observers, Engel[3] and Meyer,[4] have been able to associate their cases with the pollination of certain plants. Hence the emphasis is placed on the discovery of associated infections, such as brucellosis, trichiniasis, amebiasis, ascariasis, ancylostomiasis, etc. Rarer diseases, such as periarteritis nodosa and Hodgkin's disease, are uually mentioned and ruled out by the clinical course.

However, other causes of transient pulmonary infiltration should be kept in mind. Thus, atypical virus pneumonia may have many points in common with Loeffler's syndrome, such as x-ray findings, mildness of symptoms, and paucity of physical findings in the chest. Emphasis is placed mainly on the finding of eosinophiles in Loeffler's syndrome. To complicate matters, eosinophiles in Loeffler's syndrome may be absent or depressed due to associated infection.[15] Another source of error may be that the eosinophile counts made in the usual manner from blood smears can be unreliable.[16]

Particularly when confined to the apices, the x-ray lesions of Loeffler's syndrome may be very difficult to differentiate from those of tuberculosis. Here, the clinical course is the deciding factor.

The clinical picture as described by Loeffler[1, 17] remains essentially unchanged. The chief features are:

1. Roentgenological: one or more shadows of variable structure and size are found. They may be homogenous or mottled in appearance, more or less sharply circumscribed, unilateral or bilateral. Emphasis is placed on the transiency of the lesion; originally the duration was placed at an average of three to ten days. Of late, reports have shown that the lesions may last much longer, even months. Occasional cases show evidence of pleural involvement and even of small effusions, which are not necessarily confined to the immediate vicinity of the lesion.

2. Blood eosinophiles: usually between 10 and 60 per cent. However, there is frequently no direct relationship between the developments in the lesion and the eosinophile count. A slight leucocytosis is also encountered—up to 15,000; and the sedimentation rate is usually slightly increased.

3. Paucity of general findings: These patients may complain at most of a generalized weakness for a few days. The temperature is usually normal, but may show a slight rise for a day or two. On examination of the chest, little or no acoustic changes may be encountered. Often there is only a slight impairment of the percussion note over the lesion. Occasionally crepitant râles and a

fine, scratchy rubbing may be heard. Not all patients complain of cough. Occasionally, there may be some pain of pleuritic type. Sputum is usually small in amount, and may be absent entirely. It is described as metallic in taste and yellowish mucopurulent in appearance, with a high eosinophile percentage.

The prognosis is uniformly favorable. According to Loeffler, the patients do as well in or out of bed. Reimann[18] mentions the administration of adrenalin to prevent secondary invasion with bacteria. This is questionable, and it is very difficult to find mention of such sequelae in the literature. In this connection, the possible reduction of eosinophiles by adrenalin injections may be of interest.[19] In one of the cases to be described, an attempt to investigate possible effects of adrenalin on the lesion showed no changes on plates taken half an hour afterward. Calcium[4] and Felsol[13] have been used in Europe with questionable results, as it is obviously difficult to evaluate any therapeutic agent in such an evanescent condition.

CASE REPORTS

CASE 1.—The following is a report of a case of Loeffler's syndrome in which there were two lung lesions in rapid succession. Apparently, also, there was a history of a similar episode several years before.

The patient was a 24-year-old white male, an economist. He was seen first on Nov. 2, 1944, complaining of fever (up to 100° F. orally), night sweats, fatigue, and a slight nonproductive cough for the previous four days. For the past two weeks he had felt vague pains in the left side of the chest, anterolaterally, as well as in the left shoulder and arm. The patient had been a chronic asthmatic since the age of 2 years, had had more trouble than usual during August to October, but no hay fever, and had been giving himself 0.5 c.c. of epinephrine hypodermically almost every other day during that time. He had married during the summer and moved into another apartment, and felt that some of his asthma was due to increased exposure to inhalant allergens to which he was sensitive. During the four days of his acute illness, his asthma was better, and he had not required epinephrine.

His past history revealed the following: pneumonia at 12 years of age, ill for two to three weeks. At college, "grippe" once or twice a year, in the college infirmary a week each time. He had been skin tested and found sensitive to a number of inhalants and foods, and had found that if he avoided stuffed furniture, dust, and certain foods, he would be fairly comfortable. He had never had any hyposensitization treatments. In 1940, following two months of asthma, overworking and being "run down," he developed fever, marked weakness, a moderate cough, and pains in the left side of the chest, very similar to those of his present illness. He was studied at a Tuberculosis Clinic in New Jersey, and the x-ray report at that time was as follows: "On June 11, 1940, he developed a productive exudate in the middle third of the left lung field. In three weeks this cleared up completely. He was x-rayed again on July 7, and both lungs appeared to be entirely normal."

Family history: Mother has hay fever, brother had "bronchitis" (allergic?).

Physical examination showed only a temperature of 100° F., pulse rate of 96, and scattered, sibilant râles throughout the chest. The next day (November 3) a chest plate showed "opacity involving the lower half of the upper *right* chest with sharp demarcation at the interlobar fissure between the upper and middle right lobes. There is probably a little fluid at the site. This is suggestive of an inflammatory process, with some fluid in the lower half of the right chest. Tuberculosis cannot be ruled out." (Fig. 1.) It is to be noted that his subjective complaints were limited to the left side of the chest.

Course: With bed rest, he felt better by November 5 (seventh day of illness), with very little cough, and temperature was normal. On this date, some impairment of the percussion note was obtained posteriorly over the area shown in the x-ray. By the thirteenth day of illness he was quite well, and the percussion note changes had practically cleared. X-ray

report on this date showed "the lesion has undergone considerable resolution. The dense opacity in the right upper lung is now absent. There is still, however, marked fibrosis and some infiltration at the second and third interspaces anteriorly on the right side. The appearance is that of a resolving inflammatory process, although tuberculosis cannot be ruled out" (Fig. 2). On November 25 (twenty-seven days after onset) he reported that he was back at work, although feeling rather tired in the afternoon. Some asthma had reappeared. X-ray now showed, "The lesion has undergone almost complete resolution. There is still some increase in fibrosis at the site of the lesion."

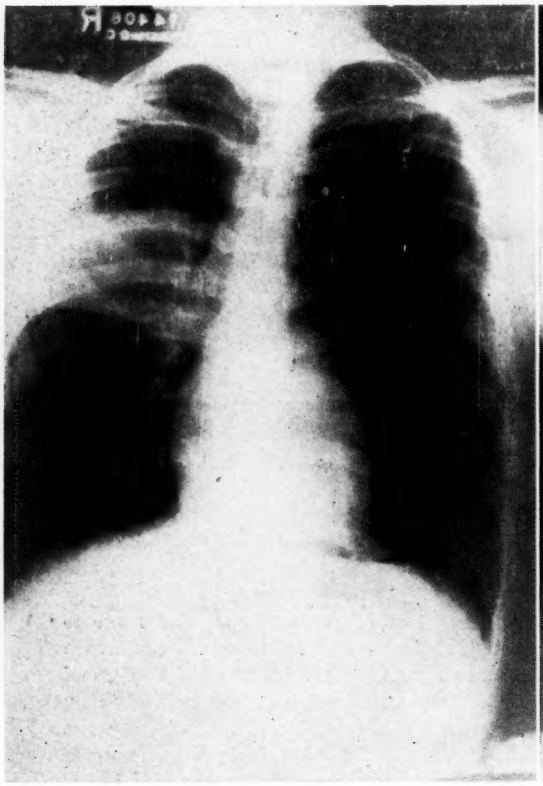

Fig. 1.

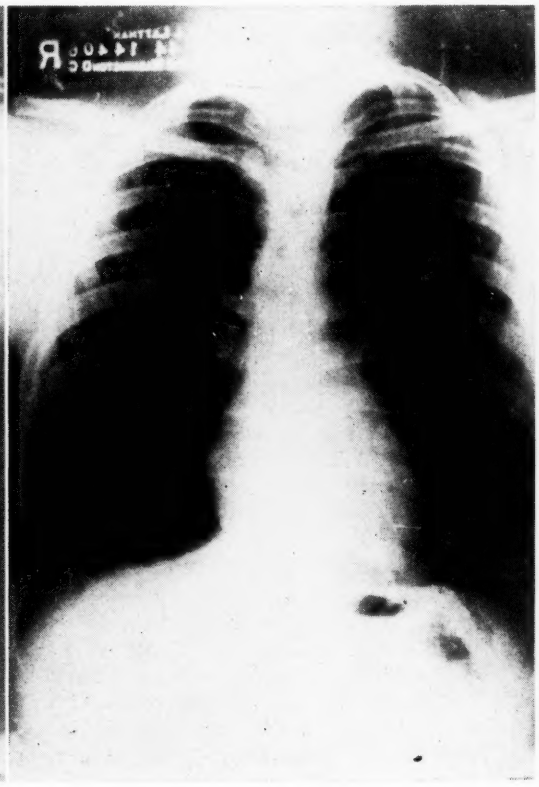

Fig. 2.

On December 7 (2 weeks after last examination) he returned with the story that until two days previously he had felt fine, but then had begun to feel tired and "dopey" and had night sweats again. His temperature had reached 101.5° F. in the afternoon. There was no cough, dyspnea, nor any of his previous chest pains. He had been having asthma, but not in the preceding five days. The only physical finding was some impairment of the percussion note over the area of the previous lesion. He was again put to bed. On December 9 (four days after recurrence) the x-rays showed "Infiltrated lesion in right chest extending from first to third interspace anteriorly—similar to previous lesion which was from second to fourth interspace" (Fig. 3).

Thereafter he showed a normal morning temperature, and afternoon temperature gradually subsiding by December 11 (sixth day of illness), with improvement in strength, but no cough at any time. On December 18 (thirteenth day of illness), x-ray showed, "Only one-half of opacity previously noted." On this date also, he was given 5 minims of epinephrine subcutaneously, and another x-ray half an hour later showed no visible change in the

lesion. Physical findings in the chest were entirely negative. By December 26 (twenty-one days after onset) he was quite well. On December 30, 1944, x-ray report was "Lesion previously reported has undergone almost complete resolution. Still considerable fibrosis in this area, suggesting a bronchitic condition, but no other evidence of pathology can be elicited" (Fig. 4).

Blood findings are described in Table I. Only one sputum specimen was obtained. This was rich in eosinophiles and negative for tubercle bacilli. Skin tests for sensitivity to allergens such as house dust made during the height of the lung lesion showed no differences from previous tests. Skin tests for trichinosis and brucellosis and a tuberculin test were negative.

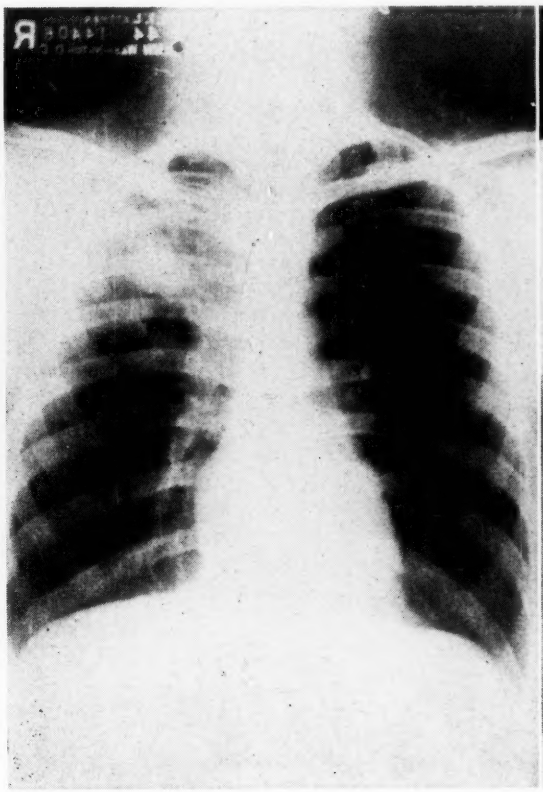

Fig. 3.

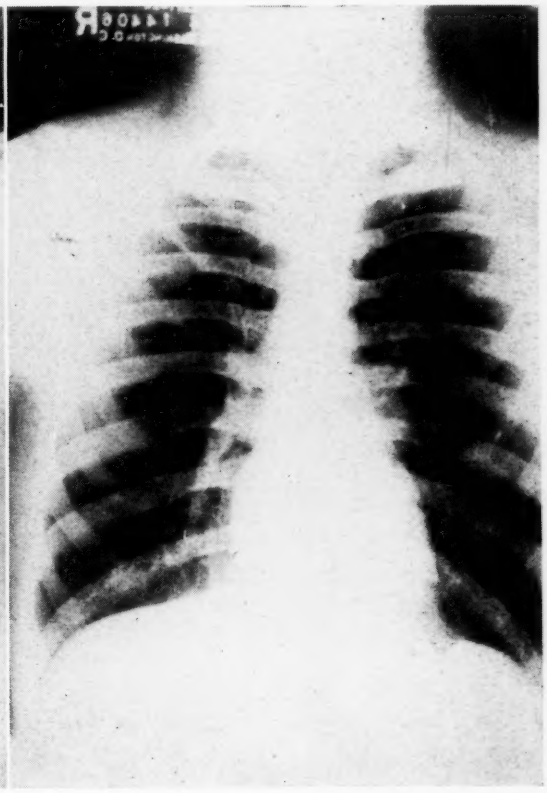

Fig. 4.

TABLE I. LABORATORY FINDINGS (CASE 1)

DATE	DAY OF ILLNESS	SEDIMENTATION RATE	TOTAL WHITE BLOOD CELLS	PER CENT OF EOSINOPHILES
11/ 3/44	5	20 mm. (Landau)	11,000	12
11/ 6/44	8			6
11/ 9/44	11	12 mm.		
11/10/44	12			6
11/14/44	16	3 mm.		8
		(Recurrence)		
12/ 9/44	4	19 mm.	12,500	2
12/16/44	11	13 mm.		2
12/26/44	21	3 mm.		1

CASE 2.—A white girl, aged 14 years, had a history of hay fever due to ragweed pollen since 1939. Routine skin testing showed moderate sensitivity to short ragweed and house dust. There was a past history of eczema in early childhood. Mother also has hay fever.

She was started on preseasonal treatment with ragweed extract in April, 1945. In June she left for a camp near Luray, Va., and was given material for injection while there. Her parents visited her there on August 19, and found that she had been coughing for a few days, with some hay fever, but was otherwise in good health. On August 23, she came back to Washington, still coughing, but otherwise feeling well. When the cough persisted, she was sent in for examination on August 29 (about two weeks after onset).

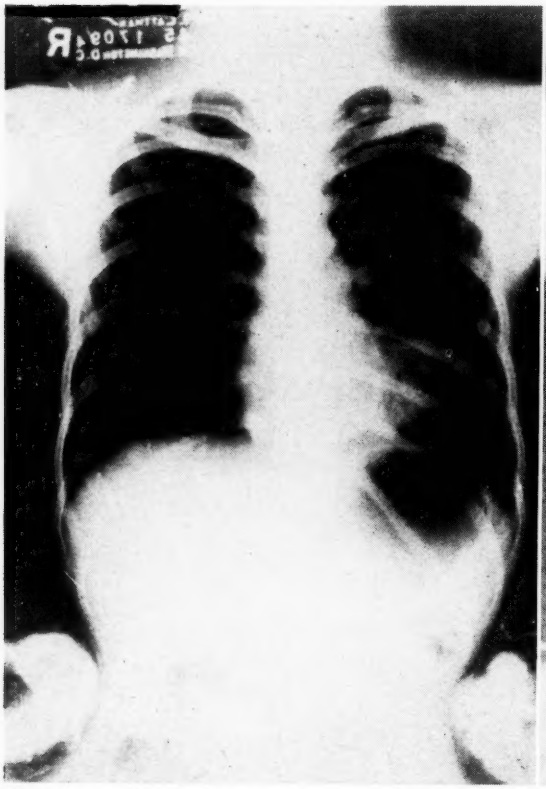

Fig. 5.

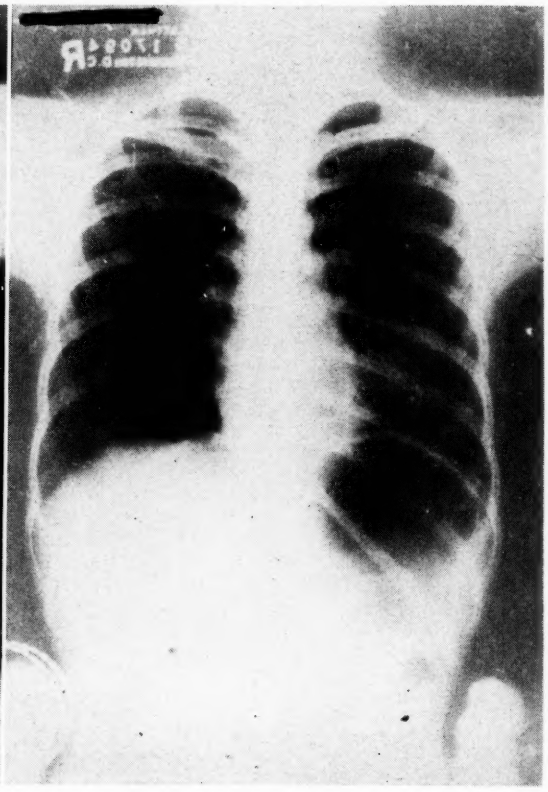

Fig. 6.

The cough was rather persistent, but dry, and she had moderate hay fever. She stated that there were no other symptoms, such as malaise, fatigue, pain in the chest, or sweats at any time. Her temperature was 99.4° F. (oral), however. Examination was otherwise negative except for the lungs. The left lung showed a slight impairment of the percussion note at the left base posteriorly, with an occasional sibilant râle, and rather distant breath sounds in this area. An x-ray report taken at this time was as follows: "An area of infiltration radiating from the mediastinum at the left base which has the appearance of an inflammatory process most likely pneumonic in nature, although a primary basilar tuberculosis should be kept in mind" (Fig. 5). She was sent home to bed. The next day her temperature was normal, and remained so. On this day also, a blood study showed a white blood cell count of 6,100, with 18 per cent eosinophiles and a sedimentation rate of 50 mm. in one hour (Wintrobe).

On September 1, two and one-half weeks after onset, the physical signs in the chest had practically disappeared, and her cough was much better. On September 3, x-ray report was "Re-examination of the chest in the anteroposterior and lateral positions as compared with previous film reveals the inflammatory process reported at the left base to have undergone considerable resolution. This, in our opinion, represents an inflammatory process rather than tuberculosis" (Fig. 6). Physical examination of the lungs was negative, and the cough had completely disappeared.

On September 9, about three and one-half weeks after onset, the x-ray showed the lesion "to have undergone marked resolution." Final x-ray on September 17 showed it to have "undergone complete resolution."

There was no treatment other than bed rest the first few days. When her second x-ray showed "considerable resolution," she was allowed up with gradual resumption of complete activity, and without any deleterious effect on recovery.

Moderate hay fever symptoms persisted throughout the entire time she was studied. Her top dose of ragweed extract given in camp was undoubtedly too low to give her much relief.

Blood findings are described in Table II. No sputum could be obtained. Skin tests for trichinosis and brucellosis, and a tuberculin test were negative.

TABLE II. LABORATORY FINDINGS (CASE 2)

DATE	DAY OF ILLNESS	SEDIMENTATION RATE	TOTAL WHITE BLOOD CELLS	PER CENT OF EOSINOPHILIA
8/29/45	14 (approx.)	50 mm. (Wintrobe)	6,000	18
9/ 1/45	17	30 mm. (Landau)		7
9/ 4/45	20	20 mm.		10
9/ 9/45	25	14 mm.		7

COMMENT

One of the most puzzling features of Loeffler's syndrome is the frequent absence of the usual phenomena accompanying lung lesions, such as cough, râles, and changes in breath sounds and percussion note. The explanation may lie in Meyenburg's pathologic findings.[2] He reports the finding of normal bronchial tubes, and, in at least one case, normal bronchioles throughout the lesion.

The cause of the frequently increased sedimentation rate, low-grade fever, and leucocytosis in these cases in the absence of proved infection may be a foreign protein reaction produced by the rapid outpouring of an exudate into the rich lung parenchyma and its rapid absorption.

Only a few reports have appeared in the foreign literature describing cases of Loeffler's syndrome ascribable to specific pollens. With the abundant and severe pollen seasons in America, one would expect to find examples of this syndrome. Many ragweed and grass sensitive cases exhibit more or less cough during the heights of these seasons, and it is possible that some of them would show x-ray or fluoroscopic evidence of transient pulmonary infiltrations. Case 2, herein reported, is believed to be such a case due to ragweed pollen, and is apparently the first such case reported.

SUMMARY

1. Two cases of Loeffler's syndrome are presented. The first, in an asthmatic patient, was characterized by two successive and recent attacks, and one prob-

able attack four years previously. The second case, in a hay fever patient, was probably due to a hitherto unreported etiologic factor, i.e., ragweed pollen.

2. The classification of known causes of this syndrome into intrinsic (infection) and extrinsic (pollens, drugs, etc.) may be useful. Recent pathologic reports may throw some light on this clinical picture.

I wish to thank Dr. Isadore Lattman for his cooperation in the preparation of this article and his interpretation of the x-rays.

REFERENCES

1. Loeffler, W.: Zur Differential-Diagnose der Lungeninfiltrierungen. I. Über fluchtige Succedan-Infiltrate (mit Eosinophilie), Beitr. z. Klin. d. Tuberk. **79**: 368-382, 1932.
2. Meyenburg, H. von: Die Pathologische Anatomie des "fluchtigen Lungeninfiltrates mit Bluteosinophilie," Virchow's Archiv. f. Path. Anat. u. Physiol. **300**: 1, 1942.
3. Engel, D.: Über eine eigenartige, anaphylaktische Erkrankung der Lunge, Beitr. z. Klin. d. Tuberk. **87**: 239-250, 1936.
4. Meyer, H. E.: Zur Kenntnis fluchtiger mit Eosinophile im Blut einhergehender Lungeninfiltrate, Med. Welt. **11**: 1808-1810, 1937.
5. Ellis, R. V., and McKinlay, C. A.: Allergic Pneumonia, J. Lab. & Clin. Med. **26**: 1427, 1941.
6. Leitner, S. J.: Hyperergic Transitory Infiltrations of the Lung Accompanied by Eosinophilia in Tuberculosis and in Abortive Pneumonias, Acta med. Scandinav. **97**: 473, 1938.
7. Elsom, K. A., and Ingelfinger, F. J.: Eosinophilia and Pneumonitis in Chronic Brucellosis: A Report of Two Cases, Ann. Int. Med. **16**: 995, 1942.
8. Hoff, A., and Hicks, H. M.: Transient Pulmonary Infiltration: A Case With Eosinophilia (Loeffler's Syndrome) Associated With Amebiasis, Am. Rev. Tuberc. **45**: 194, 1942.
9. Baumann, H.: Eosinophilic Pleurisy With Transitory Eosinophilic Pulmonary Infiltration, Schweiz. med. Wchnschr. **74**: 326, 1944.
10. Quintana, E. V.: Infiltrado de Loeffler, provocado por el Necator Americano, Rev. med.-quir. de Oriente **3**: 159, 1942.
11. Lavier, G., Bariety, M., and Caroli, J.: Distomatoses hepatique et syndrome de Loeffler, Paris med. **29**: 434, 1939.
12. Wright, D. D., and Gold, E. M.: Loeffler's Syndrome Associated With Creeping Eruption (Cutaneous Helminthiasis), J. A. M. A. **128**: 1082, 1945.
13. Braeuning, E.: Partielles Asthma? Ztschr. f. Tuberk. **73**: 174, 1935.
14. Nagel, O.: Beitr. z. Klin. d Tuberk. **96**: 185, 1941.
eosinophilie **96**: 185, 1941.
15. Jones, S. H., and Souders, C. R.: Eosinophilic Infiltration of the Lungs, New England J. Med. **231**: 356-358, 1944.
16. Feinberg, S. M.: Allergy in Practice, Chicago, 1944, Year Book Publishers, p. 416.
17. Loeffler, W.: Die fluchtigen Lungeninfiltrate mit Eosinophilie, Schweiz. med. Wchnschr. **66**: 1069-1078, 1936.
18. Reimann, H. O.: Allergic Pneumonia, Textbook of Medicine (Cecil), ed. 6, Philadelphia, 1943, W. B. Saunders Co., p. 851.
19. Campbell, T.: Relationship of Eosinophilic Response to Factors in Anaphylaxis, J. Infect. Dis. **72**: 42-48, 1943.

A CASE OF CONTACT DERMATITIS OF THE ECZEMATOUS TYPE RESULTING FROM SENSITIZATION TO NATURAL ANIMAL HAIR*

ADOLPH ROSTENBERG, JR., M.D., CHICAGO, ILL.

IT IS rather surprising, considering the number of opportunities the human has to encounter natural hair, that the incidence of contact dermatitis from it is not higher than it appears to be. From a review of the literature the number of reported cases seems to be singularly sparse. In my own experience, the case about to be reported is the first I can recollect having met. The incidence of noncutaneous reactions, primarily asthma and possibly other nasal allergies from sensitization to animal hair, appears to be considerably higher than the eczematous variety of sensitization.

Markley[1] reported the case of a woman who developed a dermatitis venenata from handling a guinea pig. Patch tests with guinea pig hair gave an erythematous vesicular reaction, but only in areas that had previously been sites of eruption. Patch tests with cat, dog, and horsehair were all negative. Kile[2] reported a case of contact dermatitis from goat hair. A woman developed a dermatitis and gave a positive patch test to mohair and undyed natural goat hair. Acetone extracts were made and a patch test with the acetone soluble portion yielded a positive reaction, whereas the test with the acetone insoluble portion was negative. The patient was treated with intramuscular injections of the acetone soluble material dissolved in almond oil, and this apparently yielded some hyposensitization. Rowe and Rogers[3] reported a case of allergic dermatitis from mohair. The lesions described and illustrated are suggestive of a contact dermatitis. The only testing done, however, was by scratch test technique with protein extracts. The patient gave a positive reaction to goat hair protein. On removal of a mohair upholstered chair, she improved. On the basis of the information, I am unable to decide whether the dermatitis was predicated on an eczematous sensitization or not. In two articles Ramirez and Eller[4, 5] mention several cases of what they term the contact type of sensitivity to various animal hairs and give the results of patch testing with these materials. From the meagerness of the description of the cases and from the fact that many of the patients also yielded positive scratch or intradermal tests with the protein extract or exhibited positive passive transfer reactions or all three, it is difficult to state whether the cases reported are of the contact or of the atopic type or represent combinations. Heiman,[6, 7] in two rather complete reviews of health hazards in the fur industry, fails to mention any cases of contact dermatitis arising as a result of sensitivity to the natural furs. While no exhaustive search of the literature was made, the above cases seem to be all that have been reported of a contact dermatitis of the eczematous type arising as the result of a sensitivity to a natural animal hair. It would, therefore, appear worth while to add a

*From the Allergy Unit and Department of Dermatology, University of Illinois College of Medicine.

case to this list, and also to point out some features of interest that can be reconstructed from the genesis of this sensitization.

CASE REPORT

V. M., a 38-year-old white woman, was seen with an intense erythematovesicular eruption primarily involving the left side of the face and neck and left arm, more marked on the volar surface. The eruption extended around the neck and was also present on the right arm and right cheek, but to a lesser degree. There were no lesions elsewhere on the body. Her past medical history was of no significance except that she was sensitive to poison ivy. The patient is the curator of a small live animal museum. A week or so previously she had obtained a new insecticide which she believed to be DDT and, after using this, the eruption had appeared rather explosively. After the skin trouble had calmed down somewhat under symptomatic therapy, I suggested we do patch tests with the insecticide. This was done and was repeated on several occasions and was always negative. This, in conjunction with the fact that her dermatitis kept flaring up despite elimination of the new insecticide, made it clear the cause was something else. Finally, after a visit to her zoo, the etiology became somewhat obvious. Incidentally, the predominantly left-sided localization had puzzled me, but I could get no clues from the history which would enable me to utilize this fact in a diagnostic fashion. On visiting the museum the patient showed me a pet coati-mundi which she was in the habit of taking out of its cage and holding so that the animal's two front paws would encircle her neck, the animal's head against her left cheek and the body crooked more or less against her left arm. Patch tests were done with the natural hair of various animals with which she came into contact (the details of the patch testing are given in Table I). A definite positive reaction was exhibited to the hair of the coati, the raccoon, and a questionable one to skunk. After telling her the results of the tests, she recalled that the coati had arrived about a week before the eruption started and also now remembered that during the course of our investigation, which, up to this point, had taken about one month, the flares were associated with the removal of this animal from its cage. She now further volunteered the information that for quite some time (the past couple of years?) whenever she would clean the raccoon cages she would feel itchy and occasionally have an evanescent skin irritation (her contact with the raccoons had never been of the intimate degree that it had been with the coati. Upon ceasing to handle the coati and exercising reasonable care when putting food in and out of the cages of the coati and raccoon she has had no further trouble. I have observed her for the past half year.

INVESTIGATORY PROCEDURES

Not knowing very much about the coati-mundi, I was quite surprised to learn that it and the raccoon belong to the same animal family. They belong to the family *Procyonidae*[8] which is a family of the *Fissipedia* (terrestrial carnivora). The *Procyonidae* include the raccoon, the ring tail cat (cacomistle or bassariscus), the kinkajou, the coati (of which there are two species or color

TABLE I. RESULTS OF PATCH TESTING*

Procyonidae or Raccoon Family		*Raccoon Hair*	
Coati, red variety	+	Acetone Ether	
Coati, gray variety†	+	Insoluble Portion	+
Kinkajou‡	0	*Coati Hair*	
Cacomistle	+		
Raccoon	++	Acetone Ether	0
		Soluble Portion	
Mustelidae or Weasel Family			
		Acetone Ether	
Skunk	+	Insoluble Portion	+
Rodentia or Rat Family		*Raccoon Hair*	
Grey Squirrel	0		
Fox	0	Washed with acetone and ether	
Guinea Pig	0	and then with water for 2 hr.	+
Hamster	0		
Spermophile	0	Material that came off in the	
Prairie Dog	0	water washing	0
White Rat	0		
White Rabbit	0	Washed with water for 2 hr.,	
		then with acetone and ether	?
Felidae or Cat Family		Material that came off in water	0
Cat, common	0	Material that came off in	
Bengal Tiger	0	acetone and ether	0
Canidae or Dog Family			
Dog, Red Setter	0		
Red Fox	0		
Primates or Monkey Family			
Rhesus Macaque	0		

*All tests were done as standard patch tests with the natural hair (except the extracts named) and were read at 48 hours, in some instances at 72 hours also.

†This was her animal.

‡One barely visible strand of hair of this animal was used in this test.

phases, namely, gray and red) and the lesser panda, which some authorities put into a separate family.

To see whether the patient would react to hairs of the other members of this family, hair was obtained from the cacomistle and the kinkajou. Hairs were also obtained from a few other species of animals.* In addition, although it had been shown that the patient definitely reacted to the hair of the coati and the raccoon, I still did not know whether she was sensitive to the hair itself or to some secretion which might sheathe the hair as from a sebaceous or other skin gland. In order to settle this point, coati hair was shaken with acetone. The mixture was then filtered, the acetone insoluble portion shaken with ether, and this mixture filtered. The two filtrates were combined and evaporated to dryness, and then made up approximately to a 3 per cent solution in acetone by weight. An identical treatment was given the raccoon hair. Patch tests were then done with the acetone soluble material and also with the acetone insoluble portions. Somewhat surprisingly, the reaction was to the acetone ether insoluble material. Various forms of washing was done and, in all instances where the patient reacted, it was to the hair itself and not to any soluble or extracted material. The details of the patch tests are given in Table I. A protein extract of the

*These were obtained through the courtesy of Mr. Perkins, Curator of the Lincoln Park Zoo, Chicago, Illinois.

coati hair was made in order to see whether the patient had any wheal type of sensitivity (although clinically there was no reason to suspect such). An intradermal test made with 0.02 c.c. was negative.

COMMENT

The patient apparently reacted to the hair of all the members of the *Procyonidae* (as I believe her negative reaction to the kinkajou hair was because of the infinitesimal quantity of the material). Her only other reaction was to skunk hair, which belongs to the Weasel family of which, unfortunately, I did not have hair from other members. It would appear that there is a common eczematous allergen in the hair of the members of the raccoon family and possibly also in the hairs of other closely related families. The protein allergens of the grasses, the pollens, and plant foods are often common to a taxonomic family or group. Among eczematous allergens this has not been established, although among the members of the *Anacardiaceae* it would seem to be true, and it has been suggested for other plant families.[9] An interesting and, to me, rather surprising fact was that the acetone soluble material did not contain the allergen (this was verified in several repetitions of the tests). From the fact that rather strenuous washing with both water and acetone plus ether failed to yield a substance to which the patient would react, it would seem that something in the hair is soluble in the materials on the skin surface or that enzymes there attack the hair yielding a substance to which the patient reacts.

In recapitulation, it would appear that the patient had developed an eczematous sensitization to raccoon hair which was either of low intensity, or the contact was not intimate enough to yield symptoms sufficiently significant to warrant attention (despite the fact that the patient had almost daily contact of some degree for several years), but when the patient met an immunologically equivalent allergen by virtue of a more intimate or a more massive exposure, she flared up with an acute incapacitating dermatitis.

SUMMARY

1. A case is reported of a woman who developed an eczematous sensitization to the natural hair of several animals, namely, coati-mundi, raccoon, and skunk.

2. The eczematous allergen of the hair seems to be common to the members of the *Procyonidae* and possibly other families.

3. The eczematous allergen was found not to be acetone or ether soluble.

REFERENCES

1. Markley, A. J.: Anaphylactoid Dermatitis Due to Direct Contact With Animal Epidermal Structures, Arch. Derm. & Syph. **2**: 722, 1920.
2. Kile, R. L.: Contact Dermatitis Due to Goat Hair, J. ALLERGY **7**: 376, 1935-36.
3. Rowe, A. H., and Rogers, H.: Allergic Dermatitis: Report of a Case Due to Mohair, California and West. Med. **23**: 1589, 1925.
4. Ramirez, M. A., and Eller, J. J.: Intradermal, Scratch, Indirect and Contact Tests in Dermatology, J. A. M. A. **95**: 1080, 1930.
5. Ramirez, M. A., and Eller, J. J.: The "Patch" Test in "Contact Dermatitis," J. ALLERGY **1**: 489, 1930.
6. Heiman, H.: Health Hazards in the Fur Industry, J. Indust. Hyg. & Toxicol. **24**: 322, 1942.
7. Heiman, H.: Health Problems in the Fur Industry, Indust. Hyg. Bull., N. Y. State Div. Ind. Hyg. **23**: 217, 1944.
8. Leister, C. W.: Present Day Mammals, New York Zoo. Soc., 1931.
9. Rostenberg, A., and Good, C. K.: Gaillardia Dermatitis, J. A. M. A. **104**: 1496, 1935.

ALLERGIC PAROTITIS

GEORGE L. WALDBOTT, M.D., AND JOHN J. SHEA, M.D., DETROIT, MICH.

CASES of recurrent swelling of the parotid gland have been reported, which indicate that it may occur on an allergic basis. In 1879 Kussmaul[1] observed a case of "fibrinous sialodochitis" which he compared with chronic fibrinous bronchitis. In the mucus from the parotid duct, Charcot-Leyden crystals were noted and "fresh pus cells" (which might have been eosinophiles, as Ehrlich's Stain was not yet used). Von Reuss[2] related a similar case in 1909 in a 16-year-old girl, characterized by eosinophilia and occurring only at the time of menses. Another girl, 8 years old, exhibited recurrent bilateral swellings of the parotid gland associated with attacks of "abdominal colic" which were suggestive of allergic intestinal disease. In 1922, Vogeler[3] reported recurrent parotid swelling, which had some resemblance to bronchial asthma. It was characterized by a blood eosinophilia of 11 per cent, by sudden appearance of the attacks, and by copious amounts of stringy mucus. The attacks terminated in what appeared to be secondary infection. In 1925, Burton-Fanning[4] observed a 62-year-old man who had recurrent attacks of sneezing, dryness of the mouth, and swelling of the parotid gland. An injection of epinephrine induced a more rapid recession of the swelling than on previous occasions. Similar instances are recorded by Barsony,[5] Wolff,[6] and von Steinitz.[7] The latter emphasized the rapidity and suddenness of the swellings and the fact that plugs of viscid mucus could be expressed on pressure over the gland. In a report by Londe and Peltz[8] in 1933 on a 10-year-old boy, no reference was made to allergy, yet the following observations made by them are of interest here: The swellings occurred in the morning and caused painful mastication. Abdominal pain preceded the attacks. Lipiodol injections showed numerous small dilatations of the salivary ducts. At no time was there fever or evidence of suppuration. The general health of the patient was not affected. Meyer[9] reported another instance in 1934 in a 6-year-old child exhibiting positive skin reactions to spinach, pork, and paprika. Upon elimination of these foods no swellings occurred for six months. Both mother and grandmother gave a history of a similar condition.

The most suggestive evidence for the allergic origin of recurrent parotid swelling was presented by Pearson.[10, 11] In 13 cases reported, some evidence of allergy was present: four had asthmatic attacks—some occurring at the time of the swellings—three had urticaria, three had hay fever, one spasmodic rhinorrhea, and there was one case of angioneurotic edema, one of eczema, and one of abdominal colic after ingestion of certain foods. There was a familial history of allergy in six.

Another such case was recorded by McCaskey,[12] in 1942, in which allergy might have been a factor. In the discussion of this paper, Hansel stated that he had seen five patients in which allergic swellings of the parotid gland occurred.

In spite of this suggestive evidence, no reference is made of this condition in the standard textbooks on allergy. It was, therefore, considered of interest to contribute the observations on the following cases.

CASE REPORTS

CASE 1.—Mr. M. H., 47 years old, had been afflicted with bronchial asthma for eighteen years. It originated while working outdoors when he was exposed to coal gas. At first the attacks were extremely severe and persistent, then they occurred periodically at two- to five-week intervals with no seasonal aggravation. During the past seven years, wheezing was present practically every night, with occasional flareups after eating certain foods, and particularly following exposure to cold air. About two years ago, following the ingestion of lima beans, a sudden swelling appeared on both cheeks, followed within twenty minutes by an asthmatic attack of unusual severity. Thereafter, practically every severe asthmatic seizure has been preceded by these swellings, sometimes bilaterally, but usually unilaterally. Within the three months preceding his admission to our office (Dec. 5, 1944) the attacks had been more frequent, resulting usually in extreme cyanosis.

Fig. 1.—Case 1. M. H. Note parotid swelling as shown by outline of ears.

The family history was negative. The past history revealed a sinus disease of long standing for which two operations had been performed in 1932 and 1941. Potatoes, doughnuts, and feathers had been recognized by the patient, in addition to lima beans, as causative agents. He had urticaria on two occasions following the ingestion of aspirin. He also believed he was sensitive to sulfonamide drugs.

Physical examination revealed the following positive findings: The nasal mucous membrane showed typical allergic edema and discoloration. There were several polyps in the left nares. Both parotid glands were enlarged, firm, and slightly tender to pressure. There was some edema at the ostium of the duct. No mucus could be expressed upon massaging the gland. The chest revealed marked emphysema, and asthmatic wheezing throughout.

After the patient had been placed on a strict dietary regime based on the skin tests and on a desensitization program for cottonseed, ragweed, yeast, house dust, rust, and some tree pollens, the attacks became much less severe and frequent. Yet, on working outdoors and after eating certain baked foods (cottonseed oil!), repeatedly marked swellings of the parotid gland, usually unilaterally and occasionally bilaterally, were noted (Fig. 1). At the termination of the attack, mucus in large amounts with numerous eosinophile cells could be expressed. At no time did the white blood count range above 7,500, nor was there any fever.

Concerning the swelling of the parotid, the patient stated that it always occurred within one-half hour before "the throat closes up" and "the chest becomes tight." The patient

was entirely free from asthma and from parotitis from July to December, 1945. He then developed an acute upper respiratory infection which precipitated moderately severe attacks of asthma without the parotid swellings. When retested in January, 1946, many of the formerly positive reacting foods were negative, while previously negative ones were positive. Cottonseed in concentrated dose gave a slightly positive reaction.

CASE 2.—Mrs. W. M., 44 years of age, was seen in October, 1940, with a history of asthma. The original attack was attributed to working in a fur shop. About six months later, she began to have swellings on both cheeks which she thought resembled "mumps." These were always followed by asthmatic seizures. The swellings were identified with the ingestion of tuna fish, lettuce, and bread. They occurred approximately every three to four weeks, and at times persisted as long as one week. On several occasions mucus could be expressed from the duct by gentle massage of the glands. Such mucus was clear, thick, tenacious, and showed considerable eosinophilia. Intradermal skin tests showed only minor reactions except for tuna fish, which was 4 plus. The other suspected antigens, namely, potatoes and wheat, as well as several furs, reacted negatively. The dust from the fur shop in which she worked reacted 2 plus on the skin. The blood eosinophile counts ranged between 6 per cent and 10 per cent. An x-ray of the parotid gland taken shortly after an attack following injection of lipiodol into the duct (Oct. 28, 1941) showed nothing unusual.* Following elimination treatment and desensitizing injections against fur dust, house dust and respiratory vaccine, the patient improved considerably; both asthma and parotid swellings disappearing.

CASE 3.—Mr. L. B., a 55-year-old farmer, was seen on Feb. 12, 1946, because of bronchial asthma. He stated that he had had periodic swellings in the areas of the parotid gland for twenty-five years, unilaterally at first and, in later years, bilaterally. They were often associated with swellings beneath the tongue. They have recently become increasingly painful, larger in size, and of longer duration. During the past four years the patient developed a great deal of nervousness, based on the fear of choking from the attacks which became more accentuated.

Since the patient was not seen during an attack, we secured the following description from his physician who attended him on several occasions: The swellings involved both parotid areas, extending far down to the neck, chin, and ears. Often the ears, chin, neck, and glands appeared to be fused into one large mass. There was uniform firmness and considerable tenderness over the whole area. No mucus could be expressed from the glands. One of these attacks required hospitalization for five days. No temperature was present during this period, nor was there any other impairment of the patient's general condition, except for an unusual degree of nervousness which could not be explained.

In June, 1945, the patient had experienced an attack of asthma for the first time, starting within a few minutes after the occurrence of the parotid swelling. This attack was attributed to contact with horses. Since then each parotid swelling was followed within a few minutes by an asthmatic attack. This occurred approximately twice a month. The patient identified the onset with the eating of certain foods which were excessively salted,† such as sauerkraut, raw onions dipped in salt, and fried salt pork. Upon discontinuing these foods, the swellings disappeared completely, but the asthma persisted.

On physical examination, the maxillary and right frontal sinuses were slightly cloudy; the nasal mucous membranes revealed some allergic edema; the pharynx was slightly reddened; the chest showed slight emphysema and some asthmatic wheezing. There was no evidence of pathologic changes on inspection and palpation of the parotid glands at the time of examination. The skin tests showed numerous moderately positive reactions to all types of antigens, including pork and onions, but none to sauerkraut. There were strong reactions to various animal hairs, which were thought to be chiefly responsible for the asthmatic attacks.

---

*Note: We did not succeed in obtaining such an x-ray at the height of the attack.

†Since we have been told of 2 other cases of parotid swellings which were attributed to the ingestion of iodides internally, sensitivity to iodized salt should be considered here.

The patient has recently returned to work on his farm, which he had not been able to do for several months. His nervousness has completely disappeared since the abatement of the swellings. It was not considered wise at this time to attempt a provocative test by having him ingest excessive amounts of salt because of the possibility of producing anaphylactic shock.

COMMENT

In these three cases there is a striking relationship of the onset of asthma with the swelling of the parotid gland. In Case 3 the recurrent swelling had been present many years before the onset of asthma, whereas in Cases 1 and 2, the asthma preceded the swellings. Food constituted the dominant cause of the attacks. There can be no doubt as to the allergic background of both the asthmatic attacks and the parotid swellings.

Whether we are dealing with an obstruction of the duct by an allergic edema or by mucus similar to that occurring in the bronchi in allergic asthma, or with an allergic edema of the glandular tissue itself is difficult to say. From the evidence at hand, we favor the former theory.

Another point in question is whether or not other cases of nonspecific recurrent parotid swelling described under the heading of infectious parotitis may not be of similar origin, the infection being superimposed, as is so often the case in many other allergic manifestations.

SUMMARY

1. Three cases of recurrent parotid swellings in asthmatics are presented. They usually occurred shortly before the onset of asthmatic seizures. In one of these patients, the swellings had been present for many years before the development of asthma.

2. Foods were definitely identified with the production of these attacks, and their elimination produced relief.

3. In view of this observation, allergy should be considered as a factor in the production of certain cases of recurrent parotitis.

REFERENCES

1. Kussmaul, I.: Anfallsweise auftretende Speichelgeschwulst in Folge von chronischer eitrig fibrinöser Entzündung des stenonschen Ganges, Berl. Klin. Wchnschr. **60**: 209-211, 1879.
2. Von Reuss, A.: Über chronische Erkrankungen der Parotis im Kindesalter, Jahrb. f. Kinderh. **70**: 161-173, 1909.
3. Vogeler, K.: Über die chronische Entzündung der Parotis, Arch. f. klin. Chir. **122**: 1922-1923, 1922.
4. Burton-Fanning, F. W.: Periodic Swelling of the Salivary Glands, Brit. M. J. **2**: 517, 1925.
5. Barsony, T.: Iodiopathische Stenongang-Dilatation, Klin. Wchnschr. **4**: 2500, 1925.
6. Wolff, S.: Über Rezidivierende Schweelungen der Parotis, Jahrb. f. Kinderh, **112**: 334-335, 1926.
7. von Steinitz, F.: Über Rezidivierende Parotisschwellungen in Kindern, Monatschr. f. Kinderh. **42**: 432-437, 1929.
8. Londe, S., and Peltz, M.: Chronic Sialodocho-Parotitis, J. Pediat. **2**: 594-602, 1933.
9. Meyer, H. S.: Chronic Sialodochitis, J. Pediat. **4**: 248-250, 1934.
10. Pearson, R. S. B.: Recurrent Swelling of the Parotid Glands, Arch. Dis. Childhood **10**: 363-376, 1935.
11. Pearson, R. S. B.: Two Cases of Recurrent Swelling of the Parotids, Guy's Hosp. Rep. **86**: 333-342, 1936.
12. McCaskey, C. H.: Chronic Nonspecific Recurring Parotitis, Tr. Am. Laryng., Rhin. & Otol. Soc. **48**: 56-61, 1942.

10 PETERBORO

CONCERNING RELIABILITY AND UNRELIABILITY OF DRIED POLLEN FROM COMMERCIAL SOURCES*†

RALPH V. ELLIS, M.D., GREENSBORO, N. C., AND
A. ORVILLE DAHL, PH.D., MINNEAPOLIS, MINN.

THE purpose of this communication is to bring to the attention of those who may be interested certain facts discovered by us concerning reliability and unreliability of dried pollen obtained from commercial sources.

In connection with investigations, extending over a period of several years[1, 2, 3, 4, 5] concerning the causes as well as the results of specific treatment of hay fever, we had occasion to examine a fairly large number of specimens of dry pollen obtained from commercial sources. Although it had been our intention, in setting up our studies, to use extracts for diagnosis and treatment prepared exclusively from pollens collected in the area wherein the patients used in these studies resided, it very early became evident that this would not be possible and we were, therefore, obliged to turn to commercial sources for these materials. Inquiries at that time revealed that only three concerns were regularly offering dry pollens for sale. Generally, we made purchases once a year calculated to supply our needs for the entire year. This was done in the following manner: a list of the kind and quantity of each pollen needed was furnished each of the three concerns, and these in turn submitted bids on each article separately. Prices fluctuated remarkably, resulting in numerous purchases from all three sources over a period of years.

Since the causes of hay fever are numerous and the cause or causes for the individual are specific, it is evident that if the data pertaining to results obtained from diagnostic or treatment procedures with pollen extracts are to be dependable, these extracts must be absolutely accurate in specificity. To insure this, all pollens used in our studies were carefully checked by microscopic examination as to identity and contamination before use in any clinical connection. Facts concerning contamination and incorrect identification resulting from these routine analyses seem sufficiently important to record. These facts would appear to have especial significance to those who are accustomed to make their own pollen extracts.

From one source (Table I, No. 2) 34 per cent of the samples showed from slight to marked contamination. Perhaps even more disconcerting is the fact that occasionally (in 17 of a total 260 samples) the pollen preparations were incorrectly identified or labeled. Microscopical preparations were made by mounting a small quantity of the pollen in filtered liquid paraffin oil. Slides were prepared in a room having no free access to air currents, and all instruments and materials were aseptically handled in order to avoid experimental contamination. Duplicate preparations and analyses were made. In most

*From the Department of Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., and the department of Botany, University of Minnesota.

†Acknowledgement is made to the Biological Laboratories, Harvard University, for research facilities.

TABLE I. SUMMARY OF PURITY AND AUTHENTICITY OF DRIED POLLEN FROM THREE DIFFERENT COMMERCIAL SOURCES

COMMERCIAL SOURCE	NUMBER OF SAMPLES EXAMINED	NUMBER AUTHENTIC AND UNCONTAMINATED	CONTAMINATED				NUMBER INCORRECTLY LABELED
			LESS THAN 1%			MORE THAN 1% (2–87%)	
			+	–	TOTAL		
1.	68	51 (75.0%)	10 (14.7%)	6 (8.8%)	16 (23.5%)	1 (1.5%)	0
2.	106	54 (50.9%)	10 (9.4%)	13 (12.3%)	23 (21.7%)	13 (12.3%)	16 (15.1%)
3.	86	72 (83.7%)	7 (8.1%)	6 (7.0%)	13 (15.1%)	0	1 (1.2%)
Total	260	177 (68.1%)	27 (10.4%)	25 (9.6%)	52 (20.0%)	14 (5.4%)	17 (6.5%)

+ = qualitatively natural contamination; – = qualitatively unnatural contamination.

cases, at least 500 pollen grains were examined. A detailed record accounting for the identity of these grains was kept.

A contaminated specimen is illustrated in Fig. 1. Several classes of contaminated samples have been indicated in Table I. Note that there is rather considerable variation in the character of the material obtained from the three sources. Serious contamination and incorrect labeling are infrequent in pollens obtained from sources 1 and 3, while lack of purity and authenticity are relatively frequent in materials from source No. 2. The slight contaminations (i.e., of the nature of 1 per cent or less) are probably of little practical importance. However, even a small contamination may involve some variety. For example, a sample of soft maple (*Acer saccharinum* L.), as shown in Fig. 1, showed a total contamination of only 0.4 per cent, and yet involved pollen grains of the birch family, chenopods, ragweeds, and pine. The chenopods and ragweeds normally begin to produce their pollen about four months after the soft maple has ceased to shed pollen.[5] Hence, the presence of these pollens in the sample is due to an artificial (preparational) cause. This type of contamination has been termed "unnatural" (–). There are, however, certain hay fever plants whose small pollen-producing flowers are surrounded by hairy or sticky structures (e.g., certain wormwoods, pigweeds, and western ragweed). These devices are capable of catching and holding other air-borne pollen grains which, in collecting procedures, become mixed with the principal constituent. Their presence as contaminants in very small quantities can be naturally accounted for. Such contamination is termed "natural" (+). A sample of cocklebur (*Xanthium*) pollen from source No. 2 was so contaminated with 0.5 per cent of common ragweed pollen.

Contaminations of a more important nature have ranged from 2 to 87 per cent and, in certain instances, involve a striking variety. Thus, a sample bearing the label "Butternut" (*Juglans cinerea* L.) pollen had the following composition:

Butternut	47.5 per cent
Hickory (*Carya*)	27.3 per cent
Plantain (*Plantago*)	7.8 per cent
Wormwood (*Artemisia*)	7.1 per cent
Birch Family (*Betulaceae*)	5.9 per cent
Grasses (*Gramineae*)	1.9 per cent
Hackberry (*Celtis*)	0.9 per cent
Pine (*Pinus*)	0.9 per cent
Chenopods (*Chenopodiales*)	0.6 per cent

Such a mixture, which involves members of eight different families, has no natural justification. Indeed, practically all trees and shrubs having reduced flowers gathered into tassel-like clusters (catkins or aments) will, with proper handling, yield very clean and pure pollen preparations. Obviously, a desensitizing extract prepared from this sample would be relatively low in the amount of sensitizing material peculiar to butternut pollen.

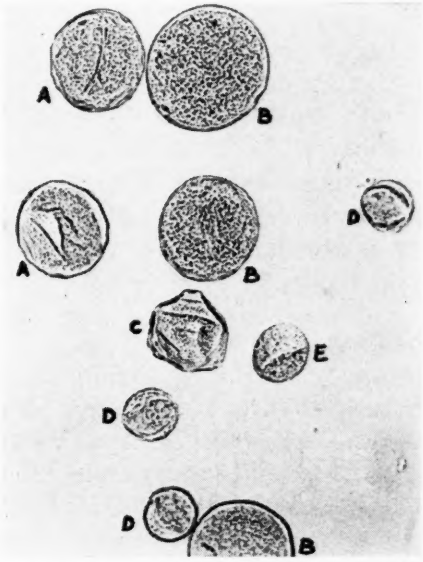

Fig. 1.—Contamination of commercially supplied pollen labeled as that of Butternut (*Juglans cinerea* L.). Identity is as follows: *A.*, Butternut pollen; *B.*, Hickory (*Carya*) pollen; *C.*, Birch (*Betulaceae*) pollen; *D.*, Wormwood (*Artemisia*) pollen; *E.*, Plantain (*Plantago*) pollen. (Unstained pollen mounted in paraffin oil, × *ca.* 325.)

TABLE II

NOTATION ON LABEL		ACTUAL IDENTITY	
PLANT	FAMILY	PLANT	FAMILY
1. Pale Dock (*Rumex*)	*Polygonaceae*	Wormwood (*Artemisia*)	*Compositae*
2. *Chenopodium leptophyllum*	*Chenopodiaceae*	Grass (Poa type)	*Gramineae*
3. Soft Maple (*Acer*)	*Aceraceae*	Poplar (*Populus*)	*Salicaceae*
4. Common Wormwood (*Artemisia*)	*Compositae*	Chenopod	*Chenopodiales*
5. Dragon Wormwood (*Artemisia*)	*Compositae*	Ragweed (*Ambrosia*)	*Compositae*
6. Basswood (*Tilia*)	*Tiliaceae*	Elm (*Ulmus*)	*Ulmaceae*
7. Sedge (*Carex*)	*Cyperaceae*	Cattail (*Typha*)	*Typhaceae*
8. Cotton wood (*Populus*)	*Salicaceae*	Tulip tree (*Liriodendron*)	*Magnoliaceae*
9. Hackberry (*Celtis*)	*Ulmaceae*	Willow (*Salix*)	*Salicaceae*
10. Ash (*Fraxinus*)	*Oleaceae*	Elm (*Ulmus*)	*Ulmaceae*

Perhaps of most serious character are the incorrectly labeled pollen preparations. The pollen supplied under a specific name may actually be that of a plant belonging to a distinctly unrelated family. In Table II are cited some of the cases of improperly labeled pollens which have been observed.

It is quite obvious that botanically unrelated families have been involved. For example, dock belongs to the buckwheat family (*Polygonaceae*) while wormwood belongs to the distinctly unrelated composite ("sunflower") family (*Compositae*).

DISCUSSION

The clinical import of these data merits further discussion.

We have repeatedly emphasized[2, 3, 4, 5] that a diagnosis of clinical sensitivity of the nose or bronchi cannot be assumed by reason by a positive skin test. When it is demonstrated that a pollen which produces a positive skin reaction in a hay fever sufferer, is a pollutant of the atmosphere coincident with that patient's symptoms, it can reasonably be presumed to be of etiologic significance. One may consider the confusion and error that may result from an incorrectly labeled or badly contaminated pollen. For example, item 2 in Table II is labeled *Chenopodium leptophyllum,* but is actually pollen from a grass of blue grass type. If the patient reacted to it, the period of symptoms would not fit the known pollination periods for the chenopod as labeled. If he did not react to it but reacted to *Chenopodium album* and other *Chenopodiaceae,* this result would be considered as evidence of differences in sensitivity to closely related species contrary to most recorded observations. If a diagnosis was made with a correctly labeled specimen of No. 8 (cottonwood) in Table II and treated with an extract of this incorrectly labeled one which is in reality tulip tree, such treatment would result in complete failure, and the method would be condemned by the patient, and certainly questioned by the physician if he had had no previous experience.

Contamination has the effect of reducing the potency of an extract. In the case of the sample of butternut pollen Vide supra the contaminants have the effect of reducing the potency of an extract to 47.5 per cent of that expected. Therefore, each 1,000 units of this extract would contain 475 units specific for butternut.

Furthermore, the possibility of establishing sensitivity to new causes of hay fever through the injection of contaminated extracts must not be overlooked.

The identification of a pollen extract is made with considerable difficulty, and the identification of contaminants in an extract is practically impossible. The identification of pollen grains is made with certainty and with relative ease by a person properly trained.

The occurrence of mislabeled or badly contaminated specimens in approximately one out of five specimens obviously indicates the importance of examination of all pollens prior to extraction. We are aware that certain of the larger pharmaceutical houses employ competent botanists for such certification

work, but we are led to wonder whether or not by some of the smaller staffed concerns, the label on the bottle of dry pollen is not taken as face value.

SUMMARY

1. By microscopic examinations of 260 different lots of dry pollen purchased from commercial sources, 68.1 per cent were found authentic and uncontaminated, 20 per cent were contaminated but slightly, and 10.4 per cent of the contamination was "natural" in character, 6.5 per cent was incorrectly labeled, and 5.4 per cent were seriously contaminated.

2. Examination for certification of dried pollen to be used for extraction should be universally required.

REFERENCES

1. Dahl, A. O., and Ellis, R. V.: The Pollen Concentration of the Atmosphere, Pub. Health Rep. **57**: 369, 1942.
2. Ellis, R. V., and Rosendahl, C. O.: A Survey of the Causes of Hay Fever for the State of Minnesota, Minnesota Med. **16**: 379, 1933.
3. Ellis, R. V., and Rosendahl, C. O.: The Diagnosis and Treatment of Hay Fever with Especial Reference to Minnesota, Minnesota Med. **17**: 378, 1934.
4. Rosendahl, C. O., and Dahl, A. O.: Causes, Diagnosis, and Treatment of Hay Fever, Minnesota Med. **19**: 505, 1936.
5. Rosendahl, C. O., Ellis, R. V., and Dahl, A. O.: Air-borne Pollen in the Twin Cities Area, With Reference to Hay Fever, Minnesota Med. **23**: 619, 1940.

Special Report

THE PATHOGENESIS OF INFANTILE ECZEMA*

Critical Review

Lewis Webb Hill, M.D., Boston, Mass.

"INTRADERMAL and scratch tests must be discarded as diagnostic procedures in eczema. The usual positive wheal reactions in infantile eczema have nothing to do with the eczema—they may be looked upon as a portent of things to come in the way of asthma or hay fever. Patch tests and clinical tests by exposure to the antigen are the only methods available to-day for etiologic diagnosis." (Quoted from R. A. Cooke.[1])

This paragraph is at variance with what many people have believed for many years. The long experience, scientific integrity, and sagacity of Dr. Cooke are such that any statement made by him warrants serious consideration, even if it does upset current conceptions. I discuss these matters in a spirit of humility, well realizing how little is accurately known about them, in an earnest desire to get at the truth, whether or not it coincides with any previous ideas I may have had.

I

"Infantile Eczema" is, in fact, dermatologically sometimes a true eczema, anatomically similar to what has been called in this country "contact dermatitis." It occurs, as a rule, however, in a particular type of individual, whose immunologic processes differ in certain respects from those of the normal person. For this reason it is called by some "atopic dermatitis." It is manifested by erythema, macules, papules, spongiosis, or vesicles as primary lesions. The mischief may be caused from within or from without, in all degrees of intensity: the vesicle is the acme.

One proposition seems to me fundamental. Erythema, maculation, papulation, spongiosis, and vesiculation arise originally from irritation of the small superficial blood vessels of the skin. Without vascular participation there can be no inflammation. Erythema is due to congestion of these vessels over a diffuse area, maculation to congestion in a small area, papulation to the escape of cells from the vessels, spongiosis and vesiculation to the escape of fluid. The terminal vessels of the skin are contained in the papillary loops, which are fingerlike projections of the corium upward into the epidermis. The epidermis itself contains no blood vessels. It therefore seems unlikely that the skin changes of infantile eczema originate in the epidermis.

*From the eczema and allergy clinic, Children's Hospital, Boston, and the Department of Pediatrics, Harvard Medical School.

The essential change in eczema is edema and cell extravasation.* (Sulzberger.[2]). If this arises from the vessels adjacent to the epidermis, the epidermal changes of eczema are produced by seepage of fluid and cells from below upwards in between the loosely packed epidermal cells; they are forced apart, and a waterlogged condition of the epidermis is produced, which is manifested on the outside surface of the skin by vesiculation or "weeping."

If vessels which lie somewhat deeper are irritated, and particularly if the irritant stimulus is sudden and violent, serum is outpoured quickly into the corium (whealing). Inasmuch as this fluid is covered by the tough tissue of the corium, there is no seepage of fluid to the surface. On the surface a raised wheal is seen, but no vesiculation or "weeping." The essential process is much the same in vesiculation and spongiosis as it is in whealing, except that in the former it goes along more slowly. "Die hyperämie und exsudation tritt langsam ein."[3] Clinical urticaria or clinical eczema occurs according to whether the escape of serum and of cells has taken place adjacent to the epidermis or further below it—suddenly or slowly.

The erythematous, papular, vesicular change produced on the skin by the patch test has its origin in the most superficial vessels; the urticarial change of the scratch or intracutaneous test arises from deeper vessels. The former takes place slowly from relatively mild irritation, the latter occurs quickly from violent irritation. There is, however, no fundamental difference between them: they are both produced by irritation of small blood vessels. The process taking place in the papillary vessels in atopic dermatitis may, therefore, as Sulzberger has said, be looked upon as subclinical whealing. It is subclinical because it takes place slowly, and because there is no roof of connective tissue over the extravasated fluid to hold it in and make a visible wheal. It is possible that too sharp a distinction has been made between atopic and contact dermatitis. The positive patch tests in atopic dermatitis, with vesicular response, obtained by Peck and Salomon,[4] by Albert and Walzer,[5] and more recently by Simon,[6] indicate this.

The classical case of contact dermatitis (ivy), with its exclusively superficial sensitization, is surely different from the classical case of atopic dermatitis with its predominating deeper sensitization. There are many variations from the classical picture, however, and it seems clear that not only infants, but many older children and adults with what has been called "chronic atopic dermatitis" and positive deep wheal reactions to "protein allergens," may have also a more superficial sensitization, not only to "protein" but to "nonprotein" allergens, and not infrequently go through episodes of acute vesicular eczema from external contact with a wide variety of allergens. This may be simply because the abraded skin becomes more easily sensitized to these allergens, or it may be that because there are multiple "atopic" sensitivities and a particular type of constitution, such a person becomes more easily sensitized to *anything* than does the normal person. I have in mind three brothers, the oldest 24, the youngest

*"The skin of the infant tends to vesiculation in a far greater degree than does the skin of the adult. I believe that in infants the epidermis is far less impermeable, not only to fluid coming from below, but also to substances coming from without. In atopic dermatitis of infants we find oozing, crusting, spongiosis and vesiculation as signs of epidermal permeability for fluids from the cutis."

9 years of age. They all had eczema as infants, two of them have hay fever now, and classical chronic atopic dermatitis of moderate degree off and on. All three have had several episodes of typical acute vesicular "contact dermatitis" from various causes.

For the reasons expressed above it seems clear that patch tests may give valid etiologic information in infantile eczema. In this I agree with Dr. Cooke. I cannot agree, however, that the urticarial type of reaction gives *no* information: the allergens which produce this reaction may produce *either* urticaria or eczema, depending upon many circumstances.

II

An urticarial and not an eczematous reaction is produced by the scratch or intracutaneous test. This has troubled a good many investigators. The following typical protocols show, it seems to me, quite clearly, that eczema can be produced from within or without by "protein" allergens, which give positive skin tests of the urticarial type. As a matter of fact, in young eczematous infants many of the positive scratch reactions to allergens which may cause dermatitis, such as milk or the cereal grains or even egg white, are manifested by erythema (the first stage of eczema) rather than by whealing. A positive intracutaneous test, on the other hand, is always manifested by whealing, because the needle goes deep into the corium.

CASE 1.—(Moro: Ekzema Infantum und Dermatitis Seborrhoides, Berlin, 1933, Julius Springer, p. 112.) A 4-month-old infant with eczema. A positive scratch test to egg white. For two days 2 c.c. of raw egg white were given with the food. There was great increase of the eczema, with much itching. No urticaria. Then egg was discontinued. In three days the eczema had subsided to its original condition.

CASE 2.—(Moro.) A child 2 years of age. The skin of this child was practically normal, but he had had eczema in certain places. He was fed 2 c.c. of raw egg white. The sites of his former eczema eruption on the arms and legs flared up with a fresh papular eruption, and great itching. When the egg white was increased to 3 c.c. and then to 5 c.c. a day, eczema appeared on the face and neck. The highest point of the reaction, with the greatest itching, was eight hours after taking egg (characteristic slow reaction time of eczema). Three days after the egg was omitted, the skin was normal again.

CASE 3.—(Moro.) In six cases Moro did patch tests with egg white, and always produced an erythematous urticarial reaction, but never eczema. Then in four cases he rubbed egg white, undiluted or in a salve, vigorously into the skin over a wide area, and produced characteristic eczema in two cases. At first there was erythema and whealing, but after four and one-half hours there appeared the beginning of a typical papular vesicular reaction, which lasted for three days (Characteristic slow reaction time of eczema).

CASE 4.—(Patient of L. W. Hill.) C. L., aged 10 months, was first seen May 28, 1936. He was breast fed until eight months of age. He began to have eczema at the age of 6 weeks. It became much worse when he was weaned. He was successively fed on "Dryco," evaporated milk, and goat's milk, without any improvement in the eczema. Examination showed a rather severe, generalized, patchy type of eczema, worse on the arms and legs.

Scratch tests were strongly positive to lactalbumin, casein, egg white, wheat, barley, rye, and pea. The reacting foods were removed from the diet: a soybean preparation was used instead of milk.

July 2, 1936. Very much better.

Sept. 17, 1936. Practically no eczema.

Jan. 28, 1937. Practically no eczema. Started milk desensitization, with a 1:1,200 milk dilution, one drop a day, to be increased 1 drop each day, up to ten days, then to begin with 1 drop of a 1:100 dilution. The eczema began to recur, when 6 drops of the first dilution was reached. Desensitization discontinued.

March 25, 1937. No eczema. Still taking soybean. At this visit an intracutaneous test with soybean was done. There was a positive reaction, the wheal measuring 0.5 cm. in diameter, with a few small pseudopods, and the usual area of erythema. Soybean feeding continued.

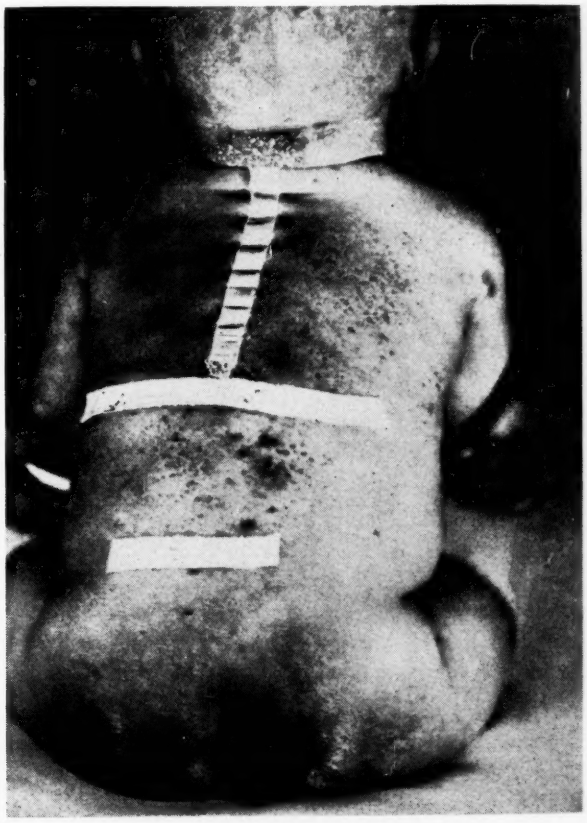

Fig. 1.—Production of eczema by rubbing egg white into the skin. Upper left—salve control; upper right—salve plus egg white; lower middle—egg white without salve. (From Moro: Ekzema Infantum und Dermatitis Seborrhoides, p. 113.)

May 6, 1937. No eczema. Milk desensitization was started again. At the end of a week a considerable amount of eczema had recurred. Desensitization discontinued.

Sept. 16, 1937. No eczema whatever. Still taking soybean.

May 26, 1938. No eczema. Desensitization started again with evaporated milk 1 drop to 3 oz. water. Five drops of this at once brought out a few small hives, and he itched all over. Desensitization discontinued. This is the only time, in the several attempts at desensitization, that hives appeared.

Dec. 1, 1938. Had hay fever in July and August, and eczema in front of the elbows. In September the eczema was better, so milk desensitization was started again. By October 1 the eczema was much worse. Desensitization discontinued.

Dec. 8, 1938. Skin normal. Positive intracutaneous test to lactalbumin 1:200,000.

Sept. 28, 1939. 3½ years old. No eczema. Desensitization to milk was started; he was taking 10 drops of undiluted milk a day with no recurrence of the eczema.

July 18, 1940. No eczema. He was given 3 teaspoonfuls of undiluted milk a day. Lost track of child after this.

Discussion.—This boy was cured of eczema by removing from his diet milk and two other foods to which he gave the urticarial type of skin test. On four different occasions, milk desensitization was attempted, and each time was followed by skin manifestations, three times by eczema, and once by hives. The hives appeared at once after taking milk, the eczema more slowly.

Although he developed a positive intradermal skin test to soybean some time after soybean feeding was started, he took this food in large quantities for approximately three years, and it caused no dermatitis. This phenomenon I have observed frequently (see THE JOURNAL OF ALLERGY **13**: 366, 1942). It is not easy to explain. The only explanation I can suggest is that soybean protein may be absorbed only for a short time after feeding with soybean is begun, and then is no longer absorbed, whereas milk protein may be absorbed over a longer period of time. This soybean reaction illustrates very well the commonly occurring intracutaneous reactions to foods, which are of no etiologic significance. It is my belief that a large proportion of positive skin tests to foods in older children and adults fall into this category.

III

Most infants with atopic dermatitis have one or more allergens to which they are violently sensitive. Egg white is the most common: fish and nuts are not uncommon. If they ingest egg white they often develop severe urticaria, swelling of the oral mucous membrane, and symptoms of shock. Eczema is caused in the natural course of events in no infant by any such allergen. After he has eaten it once it is obvious that it is no fit food for him, and he is not given it again. He may, however, develop eczema from the ingestion of allergens to which he is not violently sensitive, and which he eats every day (wheat, milk). Urticaria is a violent, sudden, explosive reaction; eczema is a more slow going, cumulative affair.

So it is quite true that such allergens as egg white, fish or nuts, which give positive wheal reactions by scratch or intracutaneous tests, and urticaria when ingested, are not ordinarily causative of the eczema. In this I agree entirely with Dr. Cooke. These violent sensitizations are present at an early age. The manner of sensitization is not entirely clear—possibly intrauterine, possibly through the breast milk, and there are cases on record which suggest that it rarely may be truly hereditary. The manner of sensitization is of no great importance in the present discussion, but I suspect that the *fact* of sensitization may be of considerable importance, and there is some reason to believe that once the baby is sensitized in high degree to egg, fish or what not, this fundamental, underlying severe primary sensitization makes him acquire more readily lesser secondary sensitizations to foods which he eats every day. The normal infant, for a short time after the ingestion of a new food, may show positive intracutaneous tests to that food. Scratch tests are not positive, and the positive intracutaneous tests last for weeks or months rather than for years. The infant who is already strongly sensitized to egg, however, possibly on account of this fact, possibly because of his particular constitution, is likely to develop positive scratch and intracutaneous tests to a wide variety of foods as they are introduced into his diet.

They are of greater intensity than those in the normal infant; they last longer, and they may or may not be accompanied by transferable antibodies. At about this time the infant begins to develop eczema. Some of his positive tests may be of etiologic significance, some may not.

One determining factor is absorption. There is great variability in the ease with which unsplit food protein is absorbed—variability in the foods, variability in the individual.

The biochemists[7] have worked this out to a certain extent, and have shown that the proteins of milk and of meat are very completely digested (95 per cent or more). The proteins of egg white are only about 85 per cent digested under the most favorable conditions. The proteins of cereals and vegetables occupy an intermediate position and show a good deal of variation. The proteins of beans and peas show a relatively low coefficient of digestibility, ranging from 70 to 80 per cent, while those of many fruits and vegetables are extremely indigestible.

This is well borne out by clinical experience. Walzer[8] has shown that, in about 80 per cent of normal persons, unsplit fish or egg protein is absorbed. It is well known that these are two of the most violent sensitivities, and that only extraordinarily small quantities may be necessary for the production of urticaria, so that, when testing for reagins, it is necessary to tell the recipient to eat no fish, egg, or nuts, or the sensitized site will react if the transferred serum contains reagins for these foods. I have seen all the sites on prepared recipients react violently from eating egg and nut, but although I have had many sites prepared with strong milk or wheat sera in adults, I have never seen these sites react following the ingestion of milk or wheat. I have repeatedly sensitized my own skin with various sera. Egg always goes through and causes the site to react if the serum has egg reagins. Once this happened from eating a piece of cookie containing egg, showing the extraordinarily small amount of ingested egg protein which will cause reaction on a sensitized skin. I have never been able to cause a reaction by the ingestion of milk or of wheat, when my own skin was sensitized with a milk or a wheat serum. Ratner and Gruehl's two cases, however, aged 12 and 9 years, show clearly that milk protein may in certain individuals go through very readily.[9]

There is need for more information on this subject. It is of vital importance to allergists.

In addition to variability in foods and in individuals, age is an important factor. While it is known that milk protein goes through with great regularity in early infancy, it does not so commonly in later childhood (Schloss), and probably even more rarely in adult life. The young infant fed on cow's milk is taking an enormous quantity of protein in relation to his weight, about 40 Gm. daily if he takes a quart of cow's milk. He was not intended by nature to take such a large amount; in a quart of human milk there is about 15 grams. Small wonder then that he may not digest it adequately, and that some is absorbed unsplit. With increasing age he takes much less milk in relation to his digestive capacities, and undigested protein is not so likely to go through. I

have records of many cases with positive milk tests where the eczema was relieved by a milk free diet, and where the child, as he grew older, could take milk with impunity, although his skin test was as large as ever. I am not certain how long such a positive test to milk persists. I have records of one case where it has lasted eight years, and is entirely without clinical significance, although it was of significance when the boy was an infant. I suspect that the majority of positive skin tests to foods in older eczematous children and adults, no matter whether by the scratch, patch, or intracutaneous method, are like this. There can be no damage to the skin by ingested food protein, if the protein does not reach the skin. This is self-evident and fundamental, and has not been given enough consideration.

For environmental allergens the situation is very different: here the mucous membrane or the skin may be so sensitized that direct contact is all that is necessary to produce symptoms. Therefore positive skin tests with environmental allergens are more likely to be of etiologic significance than those to foods, whether the clinical condition be hay fever, asthma or dermatitis. The scratch or intracutaneous tests, or the patch tests, are likely to give information which is informative. It seems certain that in the dermatitis of older children and of adults, contacts with all sorts of external substances to which either the superficial or the deeper vessels are sensitized, are of vastly more etiological importance than is the ingestion of food. The eczematous skin is a skin without resistance—it has many small open places where the protective keratin layer is gone—therefore allergens of all sorts are continually reaching sensitized tissue, and may cause not only a local, but a general exacerbation by absorption and transport to different areas. Simon's recent work with human dander is illustrative of this. There can be no doubt that it was at least partly responsible for the dermatitis in his cases, and it gave positive urticarial tests as well as positive eczematous patch tests. I would not, however, attach quite the importance to it that he does—I would consider it but one of many causes. His work, and that of Peck and Salomon and of Walzer clearly demonstrate that one and the same allergen can produce wheal reactions (urticaria), and papulo-vesicular reactions (eczema). If this is admitted, and from the evidence it must be admitted, much is explained. It does not seem to me, however, that there is anything very contradictory or extraordinary about this, or that scratch and intracutaneous tests should be discarded in infantile eczema simply because positive patch tests can sometimes be produced by the same allergen. I would not look for a mote in my brother's eye until I had examined my own for the same, and I expect that I in the past have overemphasized milk, and that Dr. Cooke and Dr. Simon are now doing the same with patch tests. Sulzberger[2] said in 1940, "It would be erroneous to conclude that one and the same substance may not, in certain instances, be capable of producing the eczematous, the urticarial, and the tuberculin type of sensitivity. All three, or any two of these forms may be associated. Urticaria and eczematous combinations are not unusual."

So let us not be in too much of a hurry to discard scratch and intracutaneous tests in infantile eczema. It seems quite clear that an allergen which produces the urticarial type of reaction can produce the eczematous type as

well. The papillary layer of the corium and the epidermis are so closely interlocked, that it is not possible to make a sharp distinction between them. In infantile eczema they are both involved. There may be erythema, macules, papules, papulo-vesicles, or vesicles, depending upon many variables. So may there be wheals, and although dermatologically speaking, I may be stretching a point, I would venture to say that whealing is a part of the entity "infantile eczema," and I have seen wheals, macules, papules and vesicles all together on the same skin at the same time, from the same cause.

I quite agree with Dr. Cooke that as far as foods are concerned, the only true criterion of etiologic significance is the production of dermatitis by ingestion of the food, and that many positive scratch or intracutaneous, and I would add patch tests, to foods, are entirely without etiologic importance. The reasons for this I have pointed out. I cannot quite go the whole way with him, however. I have seen too many eczematous infants with positive urticarial type tests to milk, wheat, or other foods cured or relieved when these foods were omitted, and have seen the eczema recur when they were resumed. I cannot ignore Moro's experiments with egg. There are surely, however, many cases of eczema in infants, and particularly in older children, which have nothing to do with wheat or milk, or with any other food, and I find myself more and more paying less attention to foods and more to the protection of the skin from external irritation of any sort whatsoever. If I had to choose between local treatment in accordance with the general principles of dermatology and immunologic treatment in accordance with the general principles of allergy, I should stick to dermatology. I should prefer, however, to combine the two.

IV

Surely, nobody understands infantile eczema: there are weak spots in the theories of everyone. When there are weak spots in the foundation, no enduring structure can be raised on it. The house is not built upon a rock. Therefore, any theory which tries to explain infantile eczema at present is not likely to be correct, for the gaps in the foundation must be filled in by ideas suggested by other facts, rather than by facts themselves.

A theory is a verified hypothesis. Therefore, one is not justified at present in formulating a theory. It seems to me, however, that from what little we do know concerning the pathogenesis of infantile eczema, the following might be looked upon as a working hypothesis, to be proved or disproved as more facts accumulate.

1. The young infant, as a rule coming from a family which is subject to hay fever, asthma, or eczema, becomes, at an early age, and before he has eczema, violently sensitized to some food, usually egg white, but possibly to some other strong sensitizer, such as fish or nuts. The mode of sensitization is either through the placenta in intrauterine life, or through the breast milk after birth. There are arguments for and against both of these modes. The main point is, however, that the sensitization is, as a rule, an extremely violent one, and that it takes place at an early age. The fact that newly born infants do not give positive skin tests to egg is not necessarily against the theory of intrauterine sensitization,

for it is well known that young animals of any kind form antibodies very poorly, and it takes them a long time to do it. It is not impossible that the infant may have been sensitized to egg in utero, and that the development of antibodies does not reach the point where skin tests or reagins can be demonstrated for some time after birth.

It has been proved that egg white can be secreted in breast milk, and thus ingested by the infant. It seems reasonable to suppose that some infants may be sensitized this way. The fact that infants who have never taken any breast milk are not uncommonly sensitized indicates that this is not the universal mode of sensitization.

2. At about the time the egg antibodies begin to be demonstrable (3 to 4 months), the baby begins to have eczema. It rarely starts before this. At this time it may also be demonstrated that there is skin sensitivity to other allergens —ingested or sometimes environmental (milk, wheat, dust, feathers).

3. Inasmuch as the infant eats no egg, it is not the cause of his dermatitis. If he is given egg in fairly large amounts experimentally he will usually react with urticaria, which will be followed by exacerbation of his eczema (quick reaction time of urticaria, slow of eczema). If he is given continued small doses of egg, under the urticaria threshold, there will be exacerbation of his eczema. If he is injected with a large amount of egg (Woringer) so that he has massive urticaria and shock, his eczema will temporarily disappear for a few days, only to recur later (antianaphylaxis).

4. This violent sensitivity, commonly to egg, and usually monovalent, may be called the *primary sensitization*. Although the food responsible for it is not causing the infant's eczema, this primary sensitization is important, for once a sensitization of high degree has become fixed in the infant, he tends more easily to become sensitized to other food and environmental allergens. The primary sensitization paves the way for secondary sensitizations, which might not occur were the primary one not present. This is the infant's admission ticket to the fraternity of the allergic.

5. The first secondary sensitizations are to foods which the infant commonly eats (milk, wheat) and to environmental allergens to which he is commonly exposed (dust, feathers). Secondary sensitizations to environmental allergens may be violent (ragweed, cat hair, horse dander). The secondary sensitizations to foods which are *eaten daily,* however, are rarely violent (milk, wheat), and these foods do not commonly cause urticaria when ingested, because the degree of sensitivity is not high enough. They cause *eczema* by repeated and continuous absorption.

6. The infant must have absorbed unsplit food protein at some time, in order to have developed a positive skin test. If, after a short time, he no longer absorbs it, which is often the case, his positive skin test is without etiologic significance. The skin test is of etiologic significance as long as he does absorb unsplit protein. The skin test may persist for a long time (years) after he has stopped absorbing unsplit protein, and the majority of positive skin tests to foods in older children and in adults are of this variety as far as eczema is

concerned. If no food protein is absorbed, no damage to the skin can result from ingestion of the corresponding food, no matter what the skin test may be.

7. Although the primary sensitization of the infant is to food, if he is exposed to environmental allergens he becomes readily sensitized to them, and they may be important factors in the causation of his eczema, either by external contact or by inhalation. The older the individual, the more important are environmental allergens, and the less important are foods.

8. In the infant, the epidermis may be involved in the inflammatory process more than the corium. Inasmuch as there are no blood vessels in the epidermis, and as there can be no inflammation independent of vascular participation, it does not seem likely that the epidermis itself is sensitized, but that the eczematous response originates in the small papillary vessels just below it.

9. An allergen, whether food or environmental, may give both scratch and patch tests, and by ingestion or by contact may produce sometimes urticaria, sometimes eczema, according to the presence or absence of many variables.

10. Infantile eczema has elements of both "atopic" and "contact" dermatitis in it. Therefore, patch tests applied to the surface of the skin may supply useful information concerning etiology. So may the urticarial type of reaction produced by scratch or intradermal tests, and they should not be discarded. There is ample proof that allergens giving this type of test can and do produce eczema as well as urticaria. The fact that these tests commonly give an urticarial and not an eczematous type of reaction is no valid argument that the allergens producing them do not, under certain conditions, produce eczema.

REFERENCES

1. Cooke, R. A.: J. ALLERGY **15**: 201, 1944.
2. Sulzberger, M.: Dermatologie Allergy, Springfield, Ill., 1940, Charles C Thomas.
3. Kreibich, C.: Handbuch der Haut und geschlechtskrankheiten, Vol. 6, p. 201, 1927.
4. Peck, S., and Salomon, G.: Am. J. Dis. Child. **46**: 1308, 1933.
5. Albert, M., and Walzer, M.: J. Invest. Dermat. **3**: 119, 1940.
6. Simon, F.: Ann. Allergy **2**: 109, 1944.
7. Mitchell, H. H., and Hamilton, T. S.: The Biochemistry of the Amino Acids, New York, 1929, The Chemical Catalog Company.
8. Walzer, M.: J. Immunol. **14**: 143. 1927.
9. Ratner, B., and Gruehl, H. L.: J. Clin. Invest. **13**: 519, 1934.

319 LONGWOOD AVENUE

Editorial

Annual Meeting of Editorial Board

At the annual meeting of the Editorial Board, two important topics were acted upon. The first concerned editorial policy. Allergy, as represented by this JOURNAL, has dealt almost entirely with that branch of the subject which is expressed in clinical practice and with investigations relevant to it. This has been the general conception of allergy among the medical profession at large, among allergists, and the laity. During the past several years there has occurred an increasing interest in the wider aspects of allergy, an interest confined at first to pathologists and immunologists, but now by enlightened internists, dermatologists, and other clinicians.

Examples of these wider implications include the work on vascular allergy by Rich and Gregory, Selye, and Klemperer, and the investigations of Landsteiner and his associates, Feinberg, and others on sensitization to simple chemicals, and newer conceptions of drug allergies as indicated by the work of Sulzberger, Black-Schreffer, and many others. The recent work of Cavelti on the hypersensitive aspect of rheumatic fever, the correlation by foreign observers of disseminated lupus erythematosus, dermatomyositis, and other members of the so-called "visceral arteritis" group, with the serum sickness syndrome and the revised ideas of the allergy of tuberculosis now under discussion are other instances of broader aspects of human hypersensitiveness.

The Editorial Board agreed unanimously that if this Journal is to express leadership in allergy, it should depart from its restricted publications and encourage and invite contributions dealing with current opinions.

The second order of business was a recognition that there was no representation on the Board of younger men. Editors were requested to bring in lists of suitable candidates, and from these four were selected: Dr. Frank Simon, Dr. Murray Albert, Dr. William Sherman, and Dr. Francis Lowell. These men are all well versed in the clinical and scientific aspects of allergy and possess literary ability. The Editorial Board welcomes them to its membership.

THE EDITOR.

American Academy of Allergy

NEWS AND NOTES

THIRD ANNUAL MEETING, HOTEL PENNSYLVANIA NEW YORK CITY

NOV. 25, 26, 27, 1946

At the third annual meeting of the American Academy of Allergy recently held in New York City, the registration was well over 650. A great deal of the credit for the success of the meeting must be given to Dr. Horace S. Baldwin and his Committee on Local Arrangements.

A new feature in the form of commercial exhibits added much to the success of the meeting. There were some thirty exhibitors—most of whom had products directly related to the practice of Allergy. The only scientific exhibit was that of the National Pollen Survey Committee, of which Mr. O. C. Durham was in charge. The program was highlighted by the presentation of Dr. Milton G. Bohrod, Pathologist, Rochester General Hospital, entitled "Allergic States and Pathologically Similar Conditions. Pathologic Differential Diagnosis." Dr. Bohrod's discussion was profusely illustrated with beautifully colored slides. It is planned that the JOURNAL OF ALLERGY will reproduce Dr. Bohrod's paper, and his slides in color. Another most significant and timely paper was by Dr. Merrill Chase of the Rockefeller Institute for Medical Research, on "Studies on the Sensitization of Animals with Simple Clinical Allergies."

The Symposium on Eczema-Dermatitis was clarifying and well received.

At the meeting of the Editorial Board of the Journal of Allergy four new members were recommended to serve on the Board. They are:

Dr. William B. Sherman, New York City
Dr. Frank Simon, Louisville, Kentucky
Dr. Murray Albert, Brooklyn, New York
Dr. Francis Cabot Lowell, Concord, Massachusetts.

This request was passed upon favorably by the Executive Committee.

Dr. Walzer presented to the Executive Committee a most ambitious plan for the formation of a Research Council of the American Academy of Allergy, to be fashioned after the Committee on Aerobiology—a division of the National Research Council. The Executive Committee approved the formation of such a Research Council which calls for the eventual formation of three major divisions:

1. Aero-allergens
2. Foods
3. Drugs and pharmaceuticals

It was directed that the president appoint a committee to organize the council and details of its functioning. It was further directed that the Division of aero-allergens be established initially—this division to be divided into several sections of subcommittees to deal with

1. Pollens
2. Molds
3. Dust and Miscellaneous allergens
4. Air processing

Men of outstanding prominence in fields related to Allergy are to have a part in this Research Council, which will undoubtedly prove to be an undertaking of great value.

At the business session of the Fellows, among other things of interest to the membership, was the announcement that the 1947 meeting of the Academy will be held at the Hotel Jefferson, St. Louis, Missouri, on Dec. 15, 16, and 17. Dr. Charles Eyermann is in charge of the Local Committee on Arrangements. Plans for the meeting are already well under way, and it would be advisable for those desiring to attend to make their hotel reservations soon.

President Bullen announced that, at the Centennial Meeting of the American Medical Association to be held at Atlantic City in June, 1947, there will be a special session on Allergy on the last afternoon of the meeting (Friday). Dr. Bullen also announced that Dr. Harry Huber had been made chairman of this Special Session, and Dr. Richard Kern, secretary. Since this special session is to be a pilot session for the Section on Allergy for which the Academy has petitioned the American Medical Association, President Bullen urged that all the Fellows and Members support this meeting by their presence. Undoubtedly, the attendance at this Special Session, the character of the program, and the interest it arouses, will have a definite bearing on whether or not a Section on Immunology and Allergy is eventually granted by the Committee on Scientific Assembly of the American Medical Association.

Several Members were elevated to full Fellowship, and one hundred forty-four new Members were added to the Academy roster.

For the Advisory Board, Dr. Cooke, explained in detail the role that the Academy's Advisory Board plays in the matter of certification. He stated that certification in the various specialties is presided over by the American Board of Medical Specialties, which is made up of some fifteen boards representing the individual specialties. Certification in Allergy is now limited to diplomates of the American Board of Internal Medicine and the American Board of Pediatrics. These diplomates are subcertified in Allergy by an examination given under the auspices of the Advisory Board of the American Academy of Allergy. Dr. Cooke pointed out that the Advisory Board of the Academy has no authority to confer certification in Allergy upon anyone, unless he first be a diplomate of the boards named and submit himself for special examination in Allergy. In the course of his remarks, Dr. Cooke referred to the fact that a number of men are dissatisfied because they were not certified in Allergy some years ago, when others were issued certification without examination. He stated that the Executive Committee was well aware of this situation, and that it had authorized the Advisory Board to request the American Board of Internal Medicine to take cognizance of this situation. Following Dr. Cooke's report for the Advisory Board, Dr. Harvey Black was elected to the Advisory Board for a six-year term, to take the place of Dr. Harry Huber, the retiring member.

Several proposed changes in the Constitution were adopted. The purpose of these changes is largely to give more men opportunity to serve on the various committees, and to take part in the activities of the Academy.

The Constitution states that a new directory shall be issued every second year. It was announced that the retiring secretary, Dr. Karl Figley, had been delegated by the president to draw up a new directory. This will include the biographical directory initiated by Dr. Spain some three years ago, after that directory has been brought up to date. It will also include a geographical roster of Fellows and Members, and the recently amended Constitution.

For the Obituary Committee, Dr. Will Spain reported as follows:

"During the past year the Academy has been unfortunate in losing four of its most distinguished members.

Dr. Arthur B. Berresford, New York City
Dr. William W. Duke, Kansas City, Missouri
Dr. Robert W. Lamson, Los Angeles, California
Dr. Charles I. Kibler, Tucson, Arizona

"Appropriate obituaries have appeared in the JOURNAL OF ALLERGY and condolences have been sent to the families of these men."

For the treasury, Dr. Criep reported that the finances of the Academy were in excellent condition. He stated that the treasurer's report had been audited by a Pittsburgh firm of accountants, and had been verified and found correct by an auditing committee appointed by the president.

For the Nominating Committee, Dr. Harry Huber, Chairman, reported the following nominees:

President	— Dr. Will C. Spain, New York City
Vice-President	— Dr. Karl D. Figley, Toledo, Ohio
Secretary	— Dr. Theodore L. Squier, Milwaukee, Wisconsin
Treasurer	— Dr. Leo H. Criep, Pittsburgh, Pennsylvania

The above slate of officers was elected by unanimous vote at the Business Session.

In closing the Business Session, Dr. Bullen called attention to the services which the retiring member of the Executive Committee—Dr. Milton B. Cohen—had rendered to the Academy over a period of many years. Dr. Bullen pointed out that Dr. Cohen had been president, and an active worker in both the parent societies of the Academy, and that he had devoted much time and effort during the past five years as a member of the Executive Committee.

The Business Session then closed with the introduction of the new president, Dr. Will Spain.

(Signed)
KARL D. FIGLEY, M.D.
Retiring Secretary

ELECTED TO FELLOWSHIP

Bernstein, Clarence, 740 North Magnolia, Orlando, Winter Park, Fla.
Dundy, Harold D., 1730 Carroll Street, Brooklyn 13, N. Y.
Friedlaender, Sidney, 18953 Appoline Street, Detroit 21, Mich.
Green, Mayer A., 6111 Jenkins Building, 500 Penn Ave., Pittsburgh 22, Pa.
Mosko, Milton M., 104 South Michigan Avenue, Chicago 3, Ill.
Prigal, Samuel J., 55 Park Avenue, New York 16, N. Y.
Randolph, Theron, 700 North Michigan Avenue, Chicago 11, Ill.

ELECTED TO MEMBERSHIP

Aaronson, Abe L., 5532 Jackson Blvd., Chicago, Ill.
Abram, Lewis E., 1561 Compton Road, Cleveland Heights, Ohio (res.)
10616 Euclid Avenue, Cleveland, Ohio (office)
Adams, Thomas J., 85-77 112th Street, Richmond Hill, N. Y.
Alexander, E. L., Suite 403, Medical Arts Building, Newport News, Va.
Altose, Richard Alexander, 903 E. Columbia St., Seattle 22, Wash.
Armour, William S., 900 20th Street South, Birmingham 5, Ala.
Aronoff, Solomon, 4000 Bergenline Ave., Union City, N. J.
Bailey, A. L., 88 Chambers Street, Greenville, Pa.
Baird, K. A., 287 King St., West St. John, N. B., Canada
Ballmer, Robert, Midland, Mich.
Banas, Charles F., 821 Cointon Street, Buffalo 10, N. Y.
Berke, Robert D. 3736 West 13th St., Chicago, Ill.
Blank, William Harvey, 909-910 Woodward Bldg., Birmingham 3, Ala.
Blue, Johnny A., 506 Hales Bldg., Oklahoma City, Okla.
Bukantz, Samuel C., Barnes Hospital, 600 So. Kingshighway, St. Louis 10, Mo.
Canseco, Carlos, Jr., Olivo 108, Col. Aguila, Tampico, Tamps, Mexico
Carliner, Paul E., 2217 South Road, Baltimore 9, Md.
Casper, Anne F., 25 Central Avenue, St. George, Staten Island, N. Y.
Catlin, R. C., 99 North Main Street, St. Albans, Vt.
Cenci, Vincent P., 50 Farmington Avenue, Hartford, Conn.

Chester Saul W., 634 Broadway, Patèrson 4, N. J.
Citron, A. Edward, 93 North Grand Avenue, Baldwin, N. Y.
Cleland, Charles E., 106 S. Fraley St., Kane, Pa.
Cohen, Stanley, 1441 Delachaise St., New Orleans, La.
Crowe, William R., 1107 Medical Arts Bldg., Atlanta, Ga.
Dees, Susan C., Duke University, Durham, N. C.
Dickstein, Bernard, 201 Dryden Bldg., Flint, Mich.
Douglas, C. L., 405 David Whitney Bldg., Detroit, Mich.
Dunn, Milton S., 310 State St., Albany, N. Y.
Egbert, O. E., 1025 First National Bank Bldg., El Paso, Texas
Ehrentheil, Otto F., 484 Commonwealth Ave., Boston, Mass.
Ehrlich, Norman James, 5009 Sheridan Road, Chicago 40, Ill.
Essex, Edward A., 2007 Madison, St., Ridgewood, N. Y.
Fenton, Meryl M., 1212 David Broderick Tower, Detroit 26, Mich.
Fischer, Louise, 31 Lincoln Park, Newark 2, N. J.
Flipse, M. Jay, 304 Huntington Bldg., Miami, Fla.
Fox, Maurice S., Allergy Laboratory, Vincennes, Ind.
Franklin, Herbert L., 41 West 96th Street, New York, N. Y.
Glasser, Benjamin F., 37-22 73rd Street, Jackson Heights, L. I.
Goodman, A. Albert, 2488 Grand Concourse, Bronx, N. Y.
Griefinger, Wm., The Medical Tower, 31 Lincoln Park, Newark 2, N. J.
Gutow, Benjamin R., 6 No. Michigan Ave., Suite 1304, Chicago 2, Ill.
Hieber, G. Frederick, Empire Bldg., St. Petersburg, Fla.
Hochfeld, Leo, 1240 Walton Avenue, New York, N. Y.
Hoffman, M. J., Medical Arts Building, 715 Lake Street, Oak Park, Ill.
Jacobs, John Lesh, 157 Peachtree St., Atlanta, Ga.
Jaros, S. H., Allergy Clinic, St. John's Hospital, Yonkers, N. Y.
Jesser, Joseph H., 522 Cornelia Ave., Chicago 13, Ill.
Johnston, C. R. Kingsley, 16089 Brewster Road, East Cleveland 12, Ohio
Kahle, Warren F., 421 Huguenot St., New Rochelle, N. Y.
Kailin, Eloise W., 2025 Eye Street, N. W., Washington 6, D. C.
Kalb, Clifford Hadleigh, 3047 No. Prospect Ave., Milwaukee, Wis.
Kalmon, Morris, 610 Second National Bldg., Akron, Ohio
Kaplan, Sidney, 1853 West Polk St., Chicago, Ill.
Keiserman, Joseph, 5460 Baltimore Ave., Philadelphia 43, Pa.
Koch, Lewis A., 62 Pierrepont St., Brooklyn 2, N. Y.
Kriendler, Louis, The Montefiore Hosp., 5th at Darragh, Pittsburgh 13, Pa.
Kurtz, I. Maxwell, 75 Martense Street, Brooklyn, N. Y.
Laws, Clarence L., Medical Arts Building, Atlanta, Ga.
Levin, Louis, 106 East 96th Street, Brooklyn, N. Y.
Levine, Jacob R., 1718 Grand Avenue, Bronx 53, N. Y.
Levitt, Harry, 137 Clinton Street, Watertown, N. Y.
Levy, Herman A., Suite 1607, 185 North Wabash Ave., Chicago, Ill.
Levy, Samuel B., 47-01 43rd Avenue, Long Island City, New York, N. Y.
Lieder, Louis E., 327 Osborn Bldg., Cleveland 15, Ohio
London, McKinley, 2813 Edgehill Road, Cleveland Heights, Ohio
Loomer, Harry P., Elmar Hotel, Los Angeles 12, Calif.
McCarthy-Brough, Marguerite, 1811 West Genesee Street, Syracuse, N. Y.
Markowitz, Benjamin F., 89 Delaware Avenue, Albany, N. Y.
Maslansky, Lawrence, 1750 Grand Concourse, New York 57, N. Y.
Miller, Ben N., 1515 Bull Street, Columbia 49, S. C.
Miller, Malcolm W., 255 South 17th St., Medical Tower Bldg., Philadelphia, Pa.
Miller, W. Lindsay, American Nat'l. Bank Bldg., Gadsden, Ala.

Millman, Milton, Seventh and Anderson Streets, Bristol, Tenn.
Moffat, Dean A., The Johns Hopkins Hospital, Baltimore 5, Md.
Morse, Leo M., Marshall Field Annex Bldg., 25 East Washington St., Chicago, Ill.
Mowry, Wm., State of Wisc. General Hospital, Madison 6, Wis.
Nachtigall, Henry B., 130 East 67th Street, New York, N. Y.
Naterman, Hyman L., 61 Huntington Road, Newton, Mass.
Necheles, John R., 55 East Washington St., Chicago 2, Ill.
Noun, Louis J., 814 Equitable Bldg., Des Moines, Iowa
O'Toole, John S., 5 Leroy St., Potsdam, N. Y.
Padnos, Emanuel, 5601 Madison Street, Chicago 44, Ill.
Parsons, D. J., 1405 East High Street, Springfield, Ohio
Paul, Andrew B., 1160 Park Avenue, New York 28, N. Y.
Pendleton, Wilson, New Medical Building, Asheville, N. C.
Perlman, Ely, Mount Sinai Hosp., Fifth Ave., and 108th St., New York 29, N. Y.
Perlman, Frank, 406 Medical Dental Bldg., Portland 5, Ore.
Peters, John, 715 Lake Street, Oak Park, Ill.
Pollack, John J., 650 Maccabee Bldg., Detroit 2, Mich.
Rand, Harold, 444 Ingraham Bldg., Miami, Fla.
Ravin, Nathan, 1185 Grant Avenue, Bronx, N. Y.
Reicher, Jacob, 357 Eastern Parkway, Brooklyn, N. Y.
Ripps, Isador, 230 East 167th St., Bronx 56, N. Y.
Rosedale, Raymond S., 610 North Market Avenue, Canton, Ohio
Rosen, Frank L., 33 Johnson Avenue, Newark, N. J.
Rosenbaum, Irving, 712 East 63rd St., Indianapolis, Ind.
Rosenbloom, Harold H., 1369 E. Hyde Park Blvd., Chicago, Ill.
Ross, Samuel, 1157 Fulton Street, Fresno 1, Calif.
Sack, S. Senior, 39-01 Main Street Flushing, N. Y.
Samter, Max, 1853 West Polk St., Chicago 12, Ill.
Sanders, Sam H., 1089 Madison Avenue, Memphis, Tenn.
Scala, R. A., 9 South Kedzie Avenue, Chicago, Ill.
Schoenkerman, Bert, 536 West Wisconsin Avenue, Milwaukee 3, Wis.
Schumacher, Irwin C., University of California Medical Center, San Francisco, 22, Calif.
Schutzbank, F. B., 4065 East Cooper St., San Clemente, Tucson, Ariz.
Schulman, Philip M., 2021 Grand Concourse, New York 53, N. Y.
Schwartz, A. B., 2018 East North Ave., Milwaukee, 2, Wis.
Schwartz, Paul M., 38 S. Clinton St., Poughkeepsie, N. Y.
Seidel, Raymond E., 1801 Porter St., Philadelphia 45, Pa.
Seidmon, Edward E., 221 West Seventh St., Plainfield, N. J.
Selser, R. E., 201 Napoleon St., Baton Rouge, La.
Shapiro, S. J., 550 Butler Road, Warren, Ohio
Shea, John J., 1919 Oakwood Boulevard, Royal Oak, Mich.
Shuey, Charles B., Medical Arts Bldg., Dallas, Texas
Shulman, M. H., 416 Marlborough St., Boston 15, Mass.
Shure, Norman Morison, 6625 Drexel Ave., Chicago, Ill.
Siegal, Sheppard, 111 East 88th St., New York 28, N. Y.
Sirmay, Elizabeth A., 672 South Westlake Avenue, Los Angeles 5, Calif.
Smith, Gadiel M., 2824 Morris Avenue, Bronx 58, N. Y.
Sochacki, A., 408 Main Street, Riverton, N. J.
Souder, Bonnell M., 206 West Seventh St., Auburn, Ind.
Steen, Wm. B., The Tucson Clinic, 110 So. Scott Street, Tucson, Ariz.
Steinhardt, Milton J., 616 Maccabees Bldg., Detroit, Mich.

Storms, Robert E., 111 East Main St., Westfield, N. Y.
Striegel, Robert Joseph, 333 Woodbridge Ave., Buffalo 14, N. Y.
Thomas, Clarence S., 512 Doctors Bldg., Nashville 3, Tenn.
Thomas, David R., Jr., Southern Finance Bldg., Augusta, Ga.
Thornhill, William A., Jr., 810 Atlas Bldg., Charleston, W. Va.
Todd, L. C., 723-731 Professional Bldg., Charlotte 2, N. C.
Traisman, Alfred S., 6349 North Clark St., Chicago 26, Ill.
Tyson, George, 458½ West Broad Street, Savannah, Ga.
Venecko, Margaret, 110 Oak St., Binghampton, N. Y.
Vicento-Mastellari, Amadeo, Calle 51, No. 26, Panama City, Rep. of Panama
Vinocur, Joseph Leonard, 10609 Euclid, Suite 305, Cleveland 6, Ohio
Vioni, R. Edward, Univ. of Ill., 1853 West Polk St., Chicago, Ill.
Walton, C. H. A., St. Mary's and Vaughan, Winnipeg, Manitoba
Warrick, George W., 900 South 20th Street, Birmingham 5, Ala.
Weil, Harry R., Milwaukee Medical Center, 525 East Michigan St., Milwaukee, Wis.
Weille, Francis L., 111 Carlton St., Brookline, Mass.
Wofford, Charles P., 505 Hamilton Bank Bldg., Johnson City, Tenn.
Wolf, Alexander
Zanfagna, Philip E., 91 Summer St., Lawrence, Mass.
Zivitz, Nelson, 311 Lincoln Road, Miami Beach, Fla.

PHYSICIANS CERTIFIED IN THE SUB-SPECIALTY OF ALLERGY, OCTOBER 1, 1946, BY THE AMERICAN BOARD OF PEDIATRICS IN COOPERATION WITH THE COMMITTEE ON ALLERGY OF THE AMERICAN BOARD OF INTERNAL MEDICINE

Schloss, Oscar M., 125 E. 72 Street, New York, N. Y.
Hill, Lewis Webb, 319 Longwood Avenue, Boston, Mass.
Buffum, William Potter, 122 Waterman Street, Providence, R. I.
Ratner, Bret, 50 East 78 Street, New York, N. Y.
Glaser, Jerome, 300 S. Goodman Street, Rochester 7, N. Y.
Fries, Joseph Harman, 25 Plaza Street, Brooklyn 17, N. Y.
Gundy, John E., 264 King Street, Port Chester, N. Y.
Horesh, Arthur J., 10515 Carnegie Avenue, Cleveland, Ohio
Levin, Samuel J., 469 Fisher Building, Detroit 2, Mich.
McGee, W. Ambrose, 1601 Monument Avenue, Richmond 20, Va.
Zohn, Benjamin, 1449 Union Street, Brooklyn 13, N. Y.
Ross, Orlando L., 9 Exchange Place, Salt Lake City, Utah

THE REPORT OF THE COMMITTEE ON PHARMACEUTICALS AND MEDICAMENTS

During the past few years, various chemical combinations having a pharmacologic effect antagonistic to histamine have been developed. Two of these have been submitted to the Committee for study and evaluation. The first was anthallan, submitted to the Committee by the Nepera Chemical Company of Yonkers, and the second product, which has been the object of a preliminary report, is pyribenzamine, manufactured by the Ciba Company.

The physicians to whom anthallan was supplied for evaluation are: Drs. Chobot, Cooke, Criep, Fromer, Sulzberger, Swineford, and Tuft.

Ninety-eight cases of ragweed hay fever were placed on anthallan, and only 3 per cent benefited. In 21 cases of perennial allergic rhinitis, only four per cent benefited. Seven cases of atopic dermatitis had a 14 per cent benefit. In the cases of urticaria, bronchial asthma, asthma and contact dermatitis, there was absolutely no evidence of clinical improvement. In 34 dermatologic cases, reported by Dr. Fromer, a 40 per cent benefit was obtained. However, Dr. Fromer states that anthallan was partially effective in the relief of itching, and that most of the patients asked to be put on pyribenzamine or something similar, but much stronger, than anthallan.

The physicians to whom pyribenzamine was supplied for evaluation are: Drs. Albert, Baer, Blumstein, Bullen, Chobot, Feinberg, Fuchs, Huber, Metzger, Prickman, Rappaport, Spain and Squier.

In the final evaluation of pyribenzamine, it was deemed wise first to divide the results according to their geographical distribution, due to the variance in the figures submitted by the various observers. It is obvious from this record that pyribenzamine is a useful palliative

TABLE I. RESULTS OF PYRIBENZAMINE THERAPY

	NO. OF CASES	IMPROVED	UNIMPROVED	PER CENT BENEFITED
Pyribenzamine Used in Addition to Pollen Therapy				
Florida Area				
Giant urticaria	100	85	15	85
Allergic rhinitis	100	16	84	16
Asthma	100	0	100	0
New York Area				
Hay fever	341	183	158	53
Asthma (all kinds)	90	16	74	17
Vasomotor rhinitis	58	18	40	32
Allergic eczema	9	4	5	44
Migraine	5	0	5	0
Urticaria (acute)	18	16	2	88
Urticaria (chronic)	13	9	4	69
Midwest Area				
Hay fever	393	327	66	83
Pollen asthma	4	0	4	0
Asthma	15	2	13	14
Urticaria	19	15	4	79
Total hay fever	834	526	308	63
Total asthma (all kinds)	209	18	191	8
Total vasomotor rhinitis (all)	58	18	40	32
Total allergic eczema	9	4	5	44
Total migraine	5	0	5	0
Total urticaria (all kinds)	150	125	25	83
Previous Preliminary Report Added to Above Figures Give the Following Totals:				
Hay fever	938	582	356	62
Asthma (all kinds)	431	88	343	20
Vasomotor rhinitis (all kinds)	335	182	153	54
Allergic eczema	18	6	12	33
Migraine	11	1	10	9
Urticaria (all kinds)	268	210	88	76
Ragweed Cases Treated With Pyribenzamine Alone				
Cases Reported in Separate Series:	89	45	44	50
Pyribenzamine With Ragweed Injections:				
Allergic rhinitis	313	235	76	75
Pollen asthma	98	47	51	48
Urticaria (acute and chronic)	154	128	26	83
Pyribenzamine Alone				
Allergic rhinitis (ragweed)	54	39	15	72
Allergic rhinitis (grasses)	12	9	3	75
Total	66	48	18	73
Combined Total of Committee Figures (With Those of Dr. Arbesman):				
Hay fever	1251	817	434	65
Asthma (all kinds)	529	135	394	26
Vasomotor rhinitis (all)	335	182	153	54
Urticaria (all kinds)	422	338	84	80
Migraine	11	1	10	9
Allergic eczema	18	6	12	33

RESULTS OF ANTIHALLAN THERAPY

CONDITION	NO. OF CASES	IMPROVED	UNIMPROVED	PER CENT BENEFITED
Ragweed hay fever	98	3	95	3
Perennial allergic rhinitis	21	1	20	4
Atopic dermatitis	7	1	6	14
Pruritus	34	23	11	40
Urticaria	5	0	5	0
Bronchial asthma	14	0	14	0
Contact dermatitis	3	0	3	0
Asthma	3	0	3	0
Total number of cases	185	28	157	15

drug in the allergic diseases characterized largely by edema, namely vasomotor rhinitis (acute, seasonal, and nonseasonal), and the urticarias. It appears to be less effective in the relief of asthma and dermatitis.

The figures indicate that, in the opinion of certain observers, pyribenzamine is quite capable of controlling symptoms in hay fever without any additional therapy. The Committee feels that the decision as to whether pollen therapy is necessary as an aid in treating these cases will be solved, not by any statistical figure, which is very difficult to estimate accurately and without bias, but rather by the hay fever patients themselves, who undoubtedly will try this medication and will settle this controversial point of their own personal experiences. The relative agreement that pyribenzamine is not too effective in any of the asthmatic conditions is an indication that the patient with pollen asthma should not be advised to discontinue pollen therapy.

It is important to remember, however, in the consideration of any of these figures, that the year 1946 was characterized by a relatively low pollen count, and it is highly problematic as to whether statistics obtained this year will apply at a time when the concentration of pollen in the air is very much greater.

Certain side effects were noted in about 30 per cent of the cases, but in no instance were these of a serious nature, and in all cases side effects were terminated with the cessation of the administration of the drug. Pyribenzamine is not a cure for allergic diseases, for in the cases studied it was necessary to continue the drug until the cause was found and removed. It is, however, an important adjuvant in the management of allergic diseases, and the Committee feels that the drug should have the approval of the Committee on Pharmaceuticals of the American Academy of Allergy, as a symptomatic aid, to be used under medical supervision in the treatment of allergic conditions.

The Committee wishes to express its appreciation for the cooperation of both the Nepera Company and the Ciba Company in submitting their products for evaluation.

Respectfully submitted,

ROBERT CHOBOT, M.D.
Chairman

REFORT OF THE COMMITTEE ON EDUCATION FOR 1946

1. The Subcommittee on Undergraduate Education with Dr. Oscar Swineford, Chairman, completed its survey of Education in Allergy in Medical Sschools begun in 1945, and the report by Dr. Swineford was published in the Journal of the Association of American Medical Colleges in September, 1946. Reprints were mailed to all known instructors in Allergy in the various medical colleges, to members of the Council on Medical Education and Hospitals of the American Medical Association, and to the editors of many medical journals.

2. A survey of the facilities for graduate study in allergy indicates 37 residencies or fellowships. Of these, only three have thus far been approved by the Council on Medical Education and Hospitals of the American Medical Association. Those not yet approved should make application immediately to the Secretary of the above-named Council, otherwise the

student may not receive credit toward certification under the American Boards of Internal Medicine or Pediatrics. All such residencies should be planned to conform with the basic requirements of these Boards.

3. Courses under the auspices of the Subcommittee on Postgraduate Education have been given as follows: January, 1946, a one-week course for specialists in Allergy was given at the New York Post-Graduate Medical School, Columbia University, with Dr. Will Cook Spain, Director. In March, 1946, a one-week course for general practitioners was given at the School of Medicine, Louisiana State University, New Orleans, with Dr. Henry Ogden, Director. A third, in October, 1946, was a one-week course for general practitioners at the Marquette University School of Medicine, Milwaukee, Wisconsin, with Dr. Theodore Squier as Director. In addition to these, several other short courses were given by Fellows of the Academy under the auspices of various Class A medical schools and the American College of Physicians.

These courses have been so well received that the Committee on Education proposes to continue to sponsor others during 1947. Announcements of these will be made in due time.

Respectfully submitted,

ROBERT A. COOKE

Chairman

NOTICE

The United States Veterans Administration is announcing an approved residency of one year in Allergy at the Veterans Administration Hospital, Aspinwall, Pa. This hospital is on a Dean's Committee, which provides regularly approved residencies in Internal Medicine.

Those interested in this position may apply to Dr. Lucien Gregg, Chairman of the Dean's Committee, School of Medicine, University of Pittsburgh.

Book Reviews

The Diagnosis and Treatment of Bronchial Asthma. By Leslie N. Gay, M.D., Baltimore, 1946, Williams and Wilkins, pp. 334, illustrated.

This is a timely contribution to the literature on allergy, for it brings the revision of ideas on classification up to date, and describes modern treatment. It is documented with relevant case reports and references, and the illustrations are appropriate. The chapters on pathology, diagnosis, and treatment of asthma are very complete; but, because the book is comparatively small, they tend to dwarf other phases of the disease. A more comprehensive presentation of the important complications of emphysema and bronchitis would be welcome. The chapter on asthmatic paroxysms due to psychosomatic disturbances is a welcome addition to any treatise on asthma.

This is a book that has a real place in the good modern literature on allergy.

It's an Allergy! By Frank G. Crandall, Jr., M.D., Hollywood, Calif., 1946, Murray and Gee, pp. 313.

The thesis of this presentation is indicated on the cover, which states that 50 per cent of the people in the United States have an allergy of some kind. This is elaborated upon throughout the text, wherein the public is made aware of the many hundreds of environmental agents which may make them ill. These are exemplified by a list of materials with which the author tests his patients. These include some 250 pollens with corresponding extensive lists of other allergens. Likewise, the number of clinical disorders attributed to allergy far exceed the usual clinical conception. Finally, there is repetition of the unusual and bizarre manifestations of allergy, as the woman who faints after eating even a very small portion of avocado.

This book is written with sincerity—almost with fervor. Unfortunately, whereas physicians recognize that the viewpoint presented is not representative of responsible allergists, the public cannot make this distinction and is exposed to a good deal of well-intended misinformation.